T-

V.12

Library

of the

Academy of Medicine

Toronto

19412

Presented by

Chicago pathological society

1928

PUBLISHERS OF LAW BOOKS
PRINTERS AND BOOKBINDERS
The Carswell Company
LIMITED
145-149 ADELAIDE STREET WEST
TORONTO

Digitized by the Internet Archive
in 2009

http://www.archive.org/details/transactions12chic

LIBRARY
DEC - 5 2002
UNIVERSITY OF TORONTO

TRANSACTIONS OF THE

Chicago Pathological Society

From June 1, 1923, to June 1, 1927

VOLUME XII

AMERICAN MEDICAL ASSOCIATION
CHICAGO: NINETEEN HUNDRED TWENTY-SEVEN

OFFICERS AND COMMITTEES

1923-1924

PRESIDENT - - - - - - - - - - - - - Lydia M. DeWitt
VICE PRESIDENT - - - - - - - - - - - - W. F. Petersen
SECRETARY - - - - - - - - - - - - George H. Weaver
TREASURER - - - - - - - - - - - - - A. A. Goldsmith

BOARD OF CENSORS

F. Robert Zeit — Walter W. Hamburger
D. J. Davis

PUBLICATION COMMITTEE

Ludvig Hektoen — H. Gideon Wells
F. Robert Zeit

1924-1925

PRESIDENT - - - - - - - - - - - - - W. F. Petersen
VICE PRESIDENT - - - - - - - - - - - - Ruth Tunnicliff
SECRETARY - - - - - - - - - - - - George H. Weaver
TREASURER - - - - - - - - - - - - - A. A. Goldsmith

BOARD OF CENSORS

F. Robert Zeit — Walter W. Hamburger
D. J. Davis

PUBLICATION COMMITTEE

Ludvig Hektoen — H. Gideon Wells
F. Robert Zeit

1925-1926

PRESIDENT - - - - - - - - - - - - - Ruth Tunnicliff
VICE PRESIDENT - - - - - - - - - - - - L. L. Arnold
SECRETARY - - - - - - - - - - - - Edwin F. Hirsch
TREASURER - - - - - - - - - - - - - A. A. Goldsmith

BOARD OF CENSORS

F. Robert Zeit — Walter W. Hamburger
D. J. Davis

PUBLICATION COMMITTEE

Ludvig Hektoen — H. Gideon Wells
F. Robert Zeit

1926-1927

PRESIDENT - - - - - - - - - - - - - - L. L. Arnold
VICE PRESIDENT - - - - - - - - - - Dallas B. Phemister
SECRETARY - - - - - - - - - - - - - Edwin F. Hirsch
TREASURER - - - - - - - - - - - - - A. A. Goldsmith

BOARD OF CENSORS

F. Robert Zeit J. J. Moore
D. J. Davis

PUBLICATION COMMITTEE

Ludvig Hektoen H. Gideon Wells
F. Robert Zeit

INDEX OF SUBJECTS AND NAMES

PAGE

Abderhalden reaction, simplified and quantitative..... 205
Abortion, pyaemia due to staphylococcus albus..... 38
Accessory food substances for yeast, the formation by B. coli communis..... 42
Acute yellow atrophy, disseminated, nodular hyperplasia of the liver following..... 135
Adenoma of the parathyroid..... 333
Agglutination, bacterial, theories on the mechanism..... 129
Agranular bronchonocardiasis..... 363
Agranulocytosis, the pathogenesis..... 360
Amyloidosis, experimental..... 142
Amyloidosis, in mice, experimental..... 206
Anaphylactic and peptone shock, the relation between blood pressure and blood volume..... 147
Anemia, sickle cell, microscopic changes..... 343
Anesthesia, surgical, the hazards with syphilis of the brain 105
Aneurysm and anomaly of the circle of Willis..... 189
Aneurysm, dissecting, of the aorta, changes at the orifices of the intercostal arteries..... 351
Aneurysm, dissecting, of the arch of the aorta, innominate and common carotid arteries with rupture into the pericardial sac..... 93
Aneurysm of the renal artery..... 333
Angina, agranulocytic, histopathology..... 143
Antigen and antibody, studies on the nature in T. B. complement fixation..... 167
Antigenic properties of bacteriophage..... 133
Antigens, distribution in the body..... 260
Antitoxin, diphtheria, the purification..... 290
Antitoxin, streptococcus erysipelatus, toxin and..... 261
Aorta, an anomalous band across the channel, at the level of the aortic leaflets..... 277
Aorta, changes at the orifices of the intercostal arteries in a dissecting aneurysm..... 351
Aorta, partially healed spontaneous incomplete rupture.. 123
Aortic arch, right, total persistence..... 353
Aortitis, primary acute..... 223
Apfelbach, Carl W..... 293

PAGE

Appendix vermiformis, carcinoid 308
Arkin, A. 353
Arnold, Lloyd 133, 219, 310

Bacillary shock, chemical alterations in the lymph 362
Bacon, Charles M. 293
Bacterial agglutination, theories on the mechanism 129
Bacterial flora and the H-ion concentration of the gastro-intestinal tract, an experimental method for study ... 219
Bactericidal mechanism, normal, of the gastro-intestinal tract. Presidential address 310
Bacteriology, pathology and immunology of generalized Torula infection 138
Bacteriophage, antigenic properties 133
Barrett, C. W. 104, 221
B. coli communis, the formation of accessory food substances for yeast 42
Bengston, John S. 338
Biggs, Alfred D. 100
Biliary passages, demonstration of specimens from an unusual carcinoma 159
Biliary tract protozoiasis 331
Biologic specificity, some observations on the relation of chemical constitution 186
Bloch, Leon 84
Blood pressure and blood volume, the relation between in anaphylactic and peptone shock 147
Blood, the rôle of the liver in maintaining the normal sugar concentration 13
Bloom, William 189
Brain, the hazard of surgical anesthesia with syphilis 105
Brams, Julius 84
Brandes, W. W. 205
Breast, female, sarcoma 367
Broman, Jessie Roberts 45
Bronchiectasis, putrid 96
Bronchonocardiasis, agranular 363
Bronchospasm, determination in the guinea-pig and certain results obtained by the method 97
Brown, Seth E. 286
B. subtilis, pathogenic, isolated from a patient having chronic tuberculosis 172
B. tuberculosis cultivated on a synthetic medium, skin reactions with the filtrate of a Koch strain 275
Bump, Warner S. 134, 289

PAGE
Caecum, cholesteatoma 143
Calcification of the mitral ring without previous infection 106
Cancer and other diseases, some misconceptions regarding the relation of heredity 225
Carcinoid of the appendix vermiformis 308
Carcinoma of aberrant thyroid gland with metastasis 148
Carcinoma of the biliary passages, demonstration of specimens from an unusual case 159
Carcinoma, primary, gelatinous, cylindrical-celled, of the lung 154
Carcinoma, primary, of the liver with hemochromatosis .. 337
Carcinoma, primary, of the trachea 45
Carcinoma, stratified squamous cell, of the body of the uterus 137
Carcinoma, transplantable rat, the effects of the short wave length, roentgen rays and diathermy 15
Cholesteatoma of the caecum 143
Circle of Willis, aneurysm and anomaly 189
Coccidioidal granuloma, skin reactions 335
Coccidioides immitis, the Ph-limits of growth and reaction changes produced in mediums 134
Coronary arteries, variations in the anastomosis and their sequences 45
Cranium, large hyperostosis due to arachnoid fibroblastoma, Mallory (so-called dural endothelioma) 340
Crowe, S. M. 26, 340
Crystalline proteins in the urine 168
Cyst, mesenteric, of the jejunum 311
Cyst, unusual parovarian (persistent Wolffian duct) 143
Cystic, kidneys 361
Cystic, liver and kidneys 353

Day, L. Enos 151, 338
Dewey, Kaethe W. 314
DeWitt, Lydia M. 1
Diabetes insipidus associated with syphilis of the hypophysis 206
Diathermy and the short wave length roentgen rays, the effects on transplantable rat carcinoma 15
Diphtheria antitoxin, the purification 290
Diphtheria toxin, the purification and nature 361
Diplococcus in measles. Presidential address 181
Ducrey bacillus isolation from the smegma of thirty men 84
Duodenum, lymph endothelioma 84

PAGE
Echinococcus disease of vertebrae and kidney with compression myelitis ... 184
Electrodialysis, fractionation of immune serum ... 139
Elliott, Arthur R. ... 100
Emmel, V. E. ... 308
Endocardium, fibromyxoma ... 347
Endothelioma, lymph, of the duodenum ... 84
Endothelioma of the posterior lobe of the hypophysis ... 95
Endothelium and the leukocytes in tissue cultures ... 164
Epithelioma, adamantine ... 289

Falk, I. S. ... 129
Fat replacement of the glycogen in the liver as a cause of death ... 199
Fibroblastoma, arachnoid, Mallory (so-called dural endothelioma), with large hyperostosis of the cranium ... 340
Fibroma of the right ovary and tortion of the left fallopian tube with spontaneous amputation ... 221
Fibromyxoma of the endocardium ... 347
Fink, E. B. ... 206, 359
Fisher, N. F. ... 351
Food poisoning in the United States ... 32
Foot and mouth disease ... 151
Fractionation of immune serum by electrodialysis ... 139
Fundamental harmony shown in all essentials in spontaneous neoplasms and in true experimental tumors ... 59
Fusospirochetal abscess of the tonsils ... 220

Gastro-intestinal tract, an experimental method for the study of bacterial flora and the H-ion concentration ... 219
Gastro-intestinal tract, the normal bactericidal mechanism 310
Gasul, B. M. ... 106
Gaucher's disease and lipoid histiocytosis ... 189
Geiger, J. C. ... 32
Glycogen in the liver, fat replacement of as a cause of death ... 199
Glycogen in tubercles, the source ... 257
Gonococcus toxin, skin reactions ... 287
Guy, Chester C. ... 333

Heart, congenital perforate interventricular septum accompanied by a shortened medial tricuspid leaflet and a dilated pulmonary artery with two cusps ... 279
Hektoen, L. ... 260
Hemangioma of the intestine ... 84

PAGE
Hemochromatosis and primary carcinoma of the liver... 337
Hemolysin, the isolation by specific absorption..... 169
Hepatic veins, the result of mechanical obstruction..... 205
Heredity, some misconceptions regarding the relation to cancer and other diseases..... 225
Hernia of the lower ileum through a congenital mesenteric opening with acute intestinal obstruction in a new-born infant..... 335
Herrold, Russell D..... 186, 275, 287
Hibbs, D. K..... 337
Hines, Lawrence E..... 184
Hirsch, Edwin F..... 22, 137, 169, 335
Holmes, Harriet F..... 220
Homme, Owen..... 38
Huber, Harry L..... 363
Huepper, William..... 154
Hypercholesteremia, the effect on experimental tuberculosis of rabbits..... 122
Hypernephroma, primary, of the liver..... 90
Hyperostosis of the cranium due to arachnoid fibroblastoma, Mallory (so-called dural endothelioma)..... 340
Hyperplasia, disseminated nodular, of the liver following acute yellow atrophy—a demonstration..... 135
Hypertrophy, congenital, of the verumontanum as a cause of urinary retention..... 172
Hypophysis, an endothelioma of the posterior lobe..... 95
Hypophysis, diabetes insipidus associated with syphilis.. 206

Ileum, acute intestinal obstruction in a new-born infant from hernia, through a congenital mesenteric opening 335
Immune serum, fractionation by electrodialysis..... 139
Immunology, pathology and bacteriology of generalized Torula infection..... 138
Intestinal obstruction, acute, in a new-born infant from hernia of the lower ileum through a congenital mesenteric opening..... 335
Intestine, hemangioma..... 84
Irradiation, tissue changes following..... 137
Ivy, A. C..... 148

Jackson, Harry..... 360
Jacques, Lawrence..... 189
Jaffé, R. H..... 122, 142, 206, 345
Jejunum, mesenteric cyst..... 311
Jones, C. K..... 340

PAGE
Kaplan, Bertha 138, 261
Kidney, compression myelitis secondary to echinococcus disease of vertebrae 184
Kidneys, congenitally cystic 361
Kidneys, congenitally cystic with cystic liver 353
Koessler, Karl K. 97
Kolodny, Anatole 137

Lactation, leukocytes and 308
Lash, A. F. 104, 221
Latimer, Earl O. 353
Leadingham, R. S. 308
Le Count, E. R. 46, 105, 135, 199
Leiomyoma of the stomach with fatal termination 5
Leukocyte balance, splanchnoperipheral 188
Leukocytes and endothelium in tissue culture 164
Leukocytes and lactation 308
Leukocytic activity, evidence of nervous control 147
Levinson, S. A. 122
Lewis, Julian H. 97, 186
Lipoid histiocytosis and Gaucher's disease 189
Liver, a primary hypernephroma 90
Liver, disseminated nodular hyperplasia following acute yellow atrophy—a demonstration 135
Liver, fat replacement of the glycogen of as a cause of death 199
Liver, hemochromatosis and primary carcinoma 337
Liver, huge congenitally cystic and cystic kidneys 353
Liver, the rôle in maintaining the normal sugar concentration of the blood 13
Locke, A. P. 139, 169, 361
Long, Esmond R. 10, 244, 335
Lung, primary, gelatinous, cylindrical-cell carcinoma 154
Lung, syphilis of 262
Lymph, chemical alterations during bacillary shock 362
Lymphoblastoma of the stomach 84

Main, Edna Ruth 290, 361
Mammary gland, development in vitro 122
Matthews, S. A. 13
Maximow, Alexander A. 122, 164
Measles, diplococcus. Presidential address 181
Meinicke microreaction in syphilis 197

PAGE
Meroacrania, anteromedian (nosencephalus) 328
Mesenteric cyst of the jejunum 311
Milles, George 362
Mitral papillary muscle, posterior, healing spontaneous rupture 282
Mitral ring, calcification without previous infection 106
Mueller, E. F. 147
Mutation forms of the tubercle bacillus 245
Myelitis, compression, secondary to echinococcus disease of vertebrae and kidney 184

Nelson, Millard J. 148
Neoplasms, spontaneous, and true experimental tumors, their fundamental harmony in all essentials 59
Nervous control of leukocytic activity 147
Nordlander, Thure A. 38, 123

Oberhelman, H. A. 46
Osteitis deformans (Paget's osteitis, osteodystrophia fibrosa senilis Christeller-Frangenheim) 345

Parasite, tubercle, variations 357
Parasitic nodules resembling tuberculosis in the lungs of swine 338
Parathyroid, adenoma 333
Parovarian cyst (persistent Wolffian duct) 143
Pathogenesis of agranulocytosis 360
Pathology, bacteriology and immunology of generalized Torula infection 138
Peptone shock, and anaphylactic, the relation between blood pressure and blood volume 147
Perry, Ethyl B. 260
Petersen, A. J. 367
Petersen, William F. 111, 188, 362
Ph-limits of growth and reaction changes produced in mediums by Coccidioides immitis 134
Pickof, F. L. 205
Piette, Eugene C. 143
Pilot, I. 96, 104, 220, 343
Pinner, Max 167, 172, 257
Pituitary body, malignant tumors 359
Political activity of Virchow 111
Portis, Bernard 15, 311
Powders, dry, with specific immune properties, their preparation 22

PAGE
Power, F. K. ... 282
Presidential addresses ... 1, 111, 181, 310
Pribram, Ernst ... 328
Protozoiasis, biliary tract ... 331
Pseudoleukemia gastro-intestinalis ... 100
Pulmonary artery and its branches, primary sclerosis ... 293
Pyaemia due to staphylococcus albus following abortion ... 38

Raffensperger, H. B. ... 338
Rappaport, B. Z. ... 138, 223
Renal artery, aneurysm ... 333
Rhabdomyoma of the tongue ... 314
Riedel's struma of the thyroid ... 313
Ring precipitation test for syphilis, further observation ... 186
Robertson, Robert C. ... 42
Robinson, William W. ... 172
Roentgen rays, short wave length, and diathermy, the effects on transplantable rat carcinoma ... 15
Rukstinat, George J. ... 262
Rupture, healing spontaneous, of the posterior mitral papillary muscle ... 282
Rupture, partially healed spontaneous incomplete, of the aorta ... 123

Saelhof, Clarence C. ... 275
Sarcoma of the female breast ... 367
Saunders, Annymarie Petersen ... 197
Schultz, O. T. ... 313
Sclerosis, primary, of the pulmonary artery and its branches ... 293
Seibert, Florence B. ... 244
Septum, congenital perforate interventricular, of the heart accompanied by a shortened medical tricuspid leaflet and a dilated pulmonary artery with two cusps ... 279
Sickle cell anemia, microscopic changes ... 343
Simonds, J. P. ... 147, 205
Singer, Harry A. ... 105, 159, 199, 261, 333
Skin reactions with coccidioidal granuloma ... 335
Skin reactions with gonococcus toxin ... 287
Skin reactions with the filtrate of a Koch strain of B. tuberculosis cultivated on a synthetic medium ... 275
Slye, Maud ... 59, 220, 225
Smithies, Frank ... 331
Splanchnoperipheral leukocyte balance ... 188

PAGE

Spontaneous amputation with tortion of the left fallopian tube and fibroma of the right ovary 221
Staphylococcus albus following abortion, pyaemia 38
Stomach, leiomyoma with fatal termination 5
Stomach, lymphoblastoma 84
Streptococci, from chronic infections of the cervix uteri and the fallopian tubes 104
Streptococcus erysipelatus toxin and antitoxin 261
Suprarenal glands, sudden death from spontaneous bilateral hemorrhage; report of two cases 26
SWEANY, H. C. 172, 245, 357
Synthetic medium filtrate skin reactions with a Koch strain of B. tuberculosis 275
Syphilis, further observation on the ring precipitation test 186
Syphilis of the brain, the hazard of surgical anesthesia .. 105
Syphilis of the hypophysis associated with diabetes insipidus 206
Syphilis of the lung 262
Syphilis, the Meinicke microreaction 197

TALIAFERRO, W. H. 130
T. B. complement fixation, studies on the nature of antigen and antibody 167
Testicle reinfection in experimental tuberculosis, and the testicle tuberculin reaction 10
Thymus, malignant tumor with extensive metastases 286
Thyroid gland, aberrant, carcinoma with metastasis 148
Thyroid, Riedel's struma 313
Thyroid tumors, the comparative pathology 220
Tissue changes following irradiation 137
Tissue culture, the leukocytes and endothelium 164
Tongue, rhabdomyoma 314
Tonsils, fusospirochetal abscess 220
Tortion of the left fallopian tube with spontaneous amputation, and fibroma of the right ovary 221
Torula, generalized infection, the pathology, bacteriology and immunology 138
Toxin and antitoxin, streptococcus erysipelatus 261
Toxin, diphtheria, the purification and nature of 361
Toxin, gonococcus, skin reactions with 287
Trachea, primary carcinoma 45
TRAUB, H. W. 361
TRAUT, EUGENE F. 347
Trypanosome infection and resistance 130

PAGE
Tubercle bacillus, mutation forms 245
Tubercle parasite, variations 357
Tubercles, the source of glycogen 257
Tuberculin, the nature of active principle 244
Tuberculin, the testicle reaction, and testicle reinfection in experimental tuberculosis 10
Tuberculosis, chronic, associated with a pathogenic B. subtilis 172
Tuberculosis, experimental, of rabbits and the effect of hypercholesterinaemia 122
Tuberculosis simulated in the lungs of swine by parasitic nodules 338
Tumor, malignant, of the thymus, with extensive metastases 286
Tumors, malignant of the pituitary body 359
Tumors, thyroid, the comparative pathology 220
Tumors, true experimental, and spontaneous neoplasms, the fundamental harmony shown in all essentials 59
Tunnicliff, Ruth 181, 363

Urinary retention, congenital hypertrophy of the verumontanum as a cause 172
Urine, crystalline proteins 168
Uterus, stratified squamous cell carcinoma of the body .. 137

Verumontanum, congenital hypertrophy as a cause of urinary retention 172
Virchow, his political activity 111

Weaver, George H.; retiring secretary of the Society 179
Weinstein, Seymour 277, 279
Weiss, Emil 133
Welker, William H. 168
Wells, H. Gideon 5, 186, 220
Williams, J. Lisle 90, 93, 95

Yeast, the formation of accessory food substances by B. coli communis 42

LIST OF MEMBERS

Allen, Thomas D.....122 S. Michigan Boulevard
Apfelbach, Carl Wesley.....2214 Osgood Street
Arkin, Aaron.....25 E. Washington Street
Arkin, Morris L.....29 E. Madison Street
Arnold, Lloyd.....University of Illinois
Austin, Richard S.....Cincinnati General Hospital, Cincinnati, Ohio

Bacon, Chas. S.....2333 Cleveland Avenue
Bassoe, Peter.....30 N. Michigan Boulevard
Baugher, Albert H.....30 N. Michigan Boulevard
Beck, Carl.....601 Deming Place
Bevan, Arthur D.....122 S. Michigan Boulevard
Billings, Frank.....1550 N. State Parkway
Blatchford, Frank W.....Winnetka, Ill.
Bloch, Leon.....310 S. Michigan Boulevard
Bloom, Wm.....1360 E. 58th Street
Brams, Julius.....180 N. Michigan Boulevard
Broman, Martin R.....Evanston, Ill.
Brown, E. V. L.....122 S. Michigan Boulevard
Brown, Sanger.....Kenilworth Sanitarium, Kenilworth, Ill.
Bryan, John C.....5536 Sheridan Road
Buchsbaum, Maurice.....1069 Broadway, Gary, Ind.
Buhlig, Walter H.....372 Normal Parkway
Beeson, B. Barker.....7 W. Madison Street
Bunting, Chas. H.....University of Wisconsin, Madison, Wis.
Burmeister, Wm. H.....St. Joseph Hospital, 2100 Burling Street
Brennecke, Herman A.....Aurora, Ill.
Byfield, Arthur F.....104 S. Michigan Boulevard
Bowman, C. Crowell.....40 E. Erie Street

Cannon, Paul R.....Ricketts Laboratory, University of Chicago
Capps, J. A.....122 S. Michigan Boulevard
Carlson, Anton J.....University of Chicago
Carr, Jas. G.....30 N. Michigan Boulevard
Chancellor, Philip S.....197 Hot Springs Road, Santa Barbara, Calif.
Corbus, B. C.....30 N. Michigan Boulevard
Crowe, S. M.....St. Luke's Hospital
Cubbins, Wm. R.....29 E. Madison Street
Culver, Harry.....7. W. Madison Street
Curtis, Arthur H.....104 S. Michigan Boulevard
Curtis, Geo. Morris.....University of Chicago
Culbertson, Carey.....30 N. Michigan Boulevard

Dagg, Thos. L.....55 E. Washington Street
David, Vernon C.....59 E. Madison Street
Davis, Carl B.....122 S. Michigan Boulevard
Davis, David J.....University of Illinois, 508 S. Honore Street
Davis, Thos. A.....2344 W. Jackson Boulevard
Davis, Geo. G.....208 S. LaSalle Street
Davis, III, Nathan S.....460 Barry Avenue

Day, Alex A.....1504 E. 65th Street
Day, L. E.....3166 Lincoln Avenue
Dennis, Geo. J.....25 E. Washington Street
Dewey, Kaethe W., University of Illinois, College of Dentistry, ...1838 W. Harrison Street
DeWitt, Lydia M.....Pathological Laboratory, University of Chicago
Dick, Geo. F.....5 S. Wabash Avenue
Dietrich, Paul H.....620 Lincoln Street, Gary, Ind.
Dodson, John.....25 E. Washington Street

Elliott, Chas. A.....30 N. Michigan Boulevard

Falls, F. H.....University of Illinois
Fink, E. B.....1430 Lunt Avenue
Fishback, Hamilton R.....7742 Jeffery Avenue
Fishbein, Morris.....5543 Blackstone Avenue
Fogelson, Samuel J.....25 E. Washington Street
Foley, Thomas P.....25 E. Washington Street

Gardner, Stella M.....5652 Race Avenue
Gatewood, Lee C.....122 S. Michigan Boulevard
Gavin, E. F.....Waukegan, Ill.
Getty, C. O.....25 E. Washington Street
Gilmer, Thos. L.....2600 Lakeview Avenue
Giordano, Alfred S.....604 N. Main Street, South Bend, Ind.
Goldsmith, A. A.....29 E. Madison Street
Gradle, Harry S.....58 E. Washington Street
Grulee, Clifford G.....310 S. Michigan Boulevard
Gruskin, Benj.....1541 E. 60th Street
Guy, Chester C.....Cook County Hospital

Hall, Alice K.....202 Harvey Avenue, North Oak Park, Ill.
Hall, Frank J., 502 Wirthman Bldg., 31st and Troost Avenue, ...Kansas City, Mo.
Hamill, Edwin.....2901 Warren Avenue
Hamill, Ralph C.....30 N. Michigan Boulevard
Hamilton, Alice.....800 S. Halsted Street
Harris, M. L.....25 E. Washington Street
Hartmann, F. S.....4458 W. Madison Street
Hatton, Edward H.....834 Michigan Avenue, Evanston, Ill.
Heineck, A. Paul.....58 E. Washington Street
Hektoen, Ludvig.....637 S. Wood Street
Herb, Isabella C.....3543 W. Adams Street
Herrick, Jas. B.....122 S. Michigan Boulevard
Herrold, Russell D.....7 W. Madison Street
Hibbs, Wm. G.....1618 Sherwin Avenue
Hines, Lawrence E.....104 S. Michigan Boulevard
Hirsch, Edwin F.....St. Luke's Hospital
Howell, Katherine.....6830 Merrill Avenue
Huber, Harry Lee.....122 S. Michigan Boulevard
Hueper, Wilhelm.....6357 N. Oakley Avenue
Holinger, J.....5 N. Wabash Avenue

Irons, Ernest E.....5830 Stony Island Avenue

Jackson, Harry.....104 S. Michigan Avenue
Jackson, Leila.....629 S. Wood Street

Jacobson, Clara.....7556 Saginaw Avenue
Jaffe, Hermann.....Grant Hospital, 549-559 Grant Place
Jared, Vernon M.....State Laboratory Building, West Palm Beach, Fla.
Jordan, E. O.....University of Chicago

Kerr, Ellis Kirk.....820 N. Oak Park Avenue, Oak Park, Ill.
Kierulff, L. A.....3815 Ellis Avenue
Koessler, Karl.....104 S. Michigan Boulevard
Kordenat Ralph A.....920 N. Michgina Boulevard
Kretuscher, Philip H.....30 N. Michigan Boulevard
Kuh, Sydney.....30 N. Michigan Boulevard
Kuhns, Ralph H.....122 S. Michigan Boulevard
Kretschmer, Herman L.....122 S. Michigan Boulevard

Lackner, Julius E.....104 S. Michigan Boulevard
Lane, Francis.....25 E. Washington Street
Lash, Abraham F.....5401 W. Washington Street
LeCount, E. R.....1743 W. Harrison Street
Lederer, Arthur.....Edward Hines Jr. Hospital, Maywood, Ill.
Leiter, Lewis.....Rockefeller Institute, New York City
Levinson, S. A.....537 Aldine Avenue
Lewis, Dean D., The Johns Hopkins Hospital, North Broadway,
.....Baltimore, Md.
Lewis, Lulian H.....3621 S. State Street
Lieberthal, David.....410 Diversey Parkway
Lusk, Frank B.....4656 N. Paulina Street
Long, Esmond R.....University of Chicago

MacCarty, Wm. Carpenter.....Mayo Clinic, Rochester, Minn.
McGlumphy, Chas. B.....5441 Winthrop Avenue
MacKechnie, Hugh N.....25 E. Washington Street
MacLane, Cleveland.....31 N. State Street
Maximow, A.....University of Chicago
McArthur, L. L.....122 S. Michigan Boulevard
McBride, Linn F.....122 S. Michigan Boulevard
McKenna, Hugh.....104 S. Michigan Boulevard
Meling, N. C.....2354 N. Kedzie Avenue
Meyer, Jacob.....739 Independence Boulevard
Miller, J. L.....122 S. Michigan Boulevard
Miler, Margaret A.....Butterworth Hospital, Grand Rapids, Mich.
Moody, Adelbert M.....St. Francis Hospital, San Francisco, Calif.
Moore, J. J.....5 S. Wabash Avenue
Moran, Tressa R.....506 Deming Place
Mueller, George.....6325 Sheridan Road
Murphy, Lipman C.....5 S. Wabash Avenue
Moorehead, F. B.....30 N. Michigan Boulevard

Nadeau, Oscar E.....642 Fullerton Parkway
Nadler, Walter H.....3638 Sheridan Road
Neymann, Clarence A.....104 S. Michigan Boulevard
Nuzum, John W.....Augustana Hospital, 2043 Cleveland Avenue
Neal, M. Pinson.....University of Missouri, Columbia, Mo.

Oberhelman, Harry A.....104 N. Park Avenue, Oak Park, Ill.
Ochsner, E. H.....2038 Lane Court
Ormsby, Oliver S.....25 E. Washington Street
Otradovec, Jos.....7235 S. Union Avenue

Parker, Chas. A.....7 W. Madison Street
Pearlman, Samuel J.....29 E. Madison Street
Petersen, Wm. F.....1322 Astor Street
Phemister, D. B.....5624 Dorchester Avenue
Pickoff, Frederick.....3210 Hirsh Street
Pietrowicz, Stephen R.....1152 N. Ashland Avenue
Piette, N.....10 Superior Street, Oak Park, Ill.
Pilot, Isadore.....3163 Pine Grove Avenue
Pirnat, Ferdinand H.....2014 W. North Avenue
Pollock, Lewis J.....25 E. Washington Street
Portis, Bernard.....104 S. Michigan Boulevard
Portis, M. Milton.....104 S. Michigan Boulevard
Portis, Sidney A.....104 S. Michigan Avenue
Preble, R. B.....30 N. Michigan Boulevard
Prendergast, Joseph.....4458 W. Madison Street
Pribram, Ernst.....St. Elizabeth Hospital
Pusey, Brown.....7 W. Madison Street
Post, Wilbur E.....122 S. Michigan Boulevard

Ries, Emil.....30 N. Michigan Boulevard
Roberg, O. Theodore.....3812 N. Keeler Avenue
Rosenow, E. C.....Mayo Clinic, Rochester, Minn.
Rukstinat, George J.....1758 W. Harrison Street
Ryan, L.....3520 W. Jackson Boulevard

Saelhof, Clarence.....4458 W. Madison Street
Salinger, Samuel.....25 E. Washington Street
Saunders, A. M. P.....State Psycopathic Hospital
Schochet, S. S.....4716 Ellis Avenue
Schultz, Oscar T.....29th and Ellis Avenue
Semerak, C. B.....5201 Magnolia Avenue
Simonds, Jas. O., Northwestern University Medical School, 303 E. Chicago Avenue
Slaymaker, S. R.....30 S. Central Park Avenue
Singer, Harry A.....Cook County Hospital
Smithies, Frank.....920 N. Michigan Boulevard
Sonnenschein, Robt.....29 E. Madison Street
Speed, Kellogg.....122 S. Michigan Boulevard
Stevenson, Alex. F.....1510 N. Dearborn Parkway
Stangl, Red H.....620 S. 1st Street, St. Cloud, Minn.
Stone, F. Lee.....25 E. Washington Street
Stotz, Chas. F.....1954 Milwaukee Avenue
Straus, David C.....310 S. Michigan Boulevard
Straus, Sidney.....104 S. Michigan Boulevard
Strouse, Solomon.....104 S. Michigan Boulevard
Swenson, Carl G.....440 Fullerton Avenue
Sweany, Harry C.....4623 N. Keating Avenue

Tint, Louis J.....185 N. Wabash Avenue
Tonney, Frederick O.....1432 Rascher Avenue
Traub, Hugo W.....30 N. Michigan Boulevard
Tunnicliff, Ruth.....637 S. Wood Street
Traut, Eugene F.....104 N. Oak Park Ave., Oak Park, Ill.

Van Hook, Weller.....7124 Coles Avenue
Van Hoosen, Bertha.....25 E. Washington Street
Vaughan, Roger T.....30 N. Michigan Avenue

Walter, Will .....1637 Chicago Ave., Evanston, Ill.
Weatherson, John.....30 N. Michigan Boulevard
Weaver, Geo. H.....637 S. Wood Street
Webster, Ralph W.....25 E. Washington Street
Weiss, Emil.....706 S. Lincoln Street
Wells, H. Gideon.....University of Chicago
Wenstrand, D. E. W.....210 Wisconsin Street, Milwaukee, Wis.
Wilder, Wm. H.....122 S. Michigan Blvd.
Williams, John C.....4458 W. Madison Street
Williams, J. Lisle.....2201 Noyes Street, Evanston, Ill.
Williamson, Chas. S.....25 E. Washington Street
Wilson, Wm. Henry.....532 Barber Bldg., Joliet, Ill.
Woodyatt, R. T.....104 S. Michigan Boulevard

Xelowski, T. Z.....1200 N. Ashland Avenue

Yudelson, Albert B.....6153 S. Park Avenue

Zeit, F. R.....643 Garland Avenue, Winnetka, Ill.

TRANSACTIONS OF THE
CHICAGO PATHOLOGICAL SOCIETY

VOL. XII MARCH 1, 1924 NO. 1

PRESIDENTIAL ADDRESS

LYDIA M. DEWITT

I wish first to express to you my appreciation of the honor conferred upon me in electing me as your president and my earnest desire that our meetings this year may be full of interest and value.

The interest of our programs depends solely upon you, members of the organization. Pathology is such a large subject that there can be little lack of material and interesting material for presentation. When we used to think of Pathology as involving only the histology of diseased tissues, only those familiar with microscopic work could hope to add much to the interest and value of a pathologic program. But now that we include in our idea of the scope of pathology, not only the changes of tissues seen at autopsy or in surgical operations, the microscopic changes of the tissues and fluids of the diseased body, but also the chemical changes, the causes of the disease, the conditions which lead up to certain changes, the subject has become much broader in its interests. Whoever therefore studies his patients thoroughly, will devote much attention to some phase of pathology. He must study the blood and compare it with the blood of the patient in health and observe the changes that take place as the disease progresses. He must study the fluids of the body, both excretory and secretory, as well as the tissues microscopically and chemically, determining how all these differ from the normal.

No case studied in this exhaustive manner can fail to add something to our knowledge of medicine as well

as of pathology and any physician who so studies his cases, will often have something of interest to report to a society of this character. He need have little fear that his findings will give us nothing new to think about and to discuss. Every case is sure to have some points different from any other case of the same disease if only the investigation has been painstaking enough to find the points.

Perhaps no disease has been longer known and more carefully studied than tuberculosis. And yet the last fifteen years have added much to our knowledge of the disease and all its manifestations. Lawrason Brown in his presidential address before the National Tuberculosis Association at Santa Barbara last June said: Knowledge of Tuberculosis has come very slowly. It required two thousand three hundred years to prove that pulmonary tuberculosis was contagious, and even today with all our studying we can not agree upon all the details, for too much rests upon authority, too little upon ascertained facts. Much work remains to be done. For over one thousand eight hundred years it has been known that sunlight, milk, good food and mountain air are good for patients with pulmonary tuberculosis, yet modern times have made some real contributions to our knowledge of the therapy of tuberculosis. For over one hundred and fifty years, we have been able to percuss a chest and for over one hundred years we have had the stethoscope at our disposal and yet within the last fifteen years many men have written on these methods in such a way that one is led to conclude that even many specialists in pulmonary tuberculosis were long unaware of the best technique. Between 1893 and 1923 so many articles were written on tuberculosis that the mere titles and references filled over 418 pages in fine print in the Index Catalogue of the Surgeon General's Library in Washington. And he adds: Today he who adds anything new to the knowledge of tuberculosis deserves the thanks of mankind.

The fundamental character of some of these publications is well illustrated in an article recently published by Pottenger on fundamental reactions of Body Cells

in Tuberculosis. The following quotation from this gives us an idea of the scope of the study: The factors in our colloido-crystalloidal conception which seem to be disturbed by disease processes are as follows: (1) The phases of the colloidal systems which make up the normal tissues may be changed; (2) the ability of the colloids to bind or give off electrolytes may be interfered with; (3) the electrolytes which combine with the colloidal systems may not be present in normal amounts; (4) the water content of the body may be insufficient; (5) differences in surface tension may exist.

Many of the publications concern themselves with problems of immunity and complement fixation in tuberculosis. The range of subjects illustrates well the amount of experimental as well as clinical work that is being done on the subject of tuberculosis.

If there is need of all this work in a disease so long and so thoroughly studied as tuberculosis, how much greater need must there be in the many diseased conditions we have only begun to study of some of which we do not yet even know the cause and of which the pathology is quite an untrodden field.

It may well be that much of the increased activity in tuberculosis work, both medical and sociological, is closely connected with the National organization of those interested in helping the tuberculous. The organization, formed about 1904, took the name, The American Association for the Study and Prevention of Tuberculosis, a name later shortened to The National Tuberculosis Association. The meeting last June was the nineteenth annual meeting of the National Association. The Association and its programs are divided into three definite sections, clinical, pathological and sociological. The membership, as listed last year, numbered nearly 5,000. These are by no means all medical men, but they are all interested, at least to the extent of keeping up their membership dues, in helping to support the movement to blot out or diminish tuberculosis in the United States. In the 10 years, from 1911 to 1922, the death rate from tuberculosis has been said to show a decrease of 38 per cent. We can not claim that all of this fall has

been due to the antituberculosis campaign, but it is probably due in part to the measures taken in connection with the campaign. The education concerning the disease and the improved living conditions have, no doubt, had much to do with the improvement, and they are very closely associated with the organized movement. Who does not know, what child even does not know, many of the signs and symptoms of the disease and its methods of spread and its most hopeful methods of treatment? This wide distribution of information is the best known means of combating a scourge like tuberculosis.

This National Tuberculosis Association is associated with an international union against tuberculosis, which will hold its fourth meeting next year, the president being our well known Dr. Theobald Smith. These few details of the National Tuberculosis organization, combined with what you all know of the active and widespread interest in its work throughout the whole country, will suggest the possible advantage of some such an organized educational movement in the interest of public health and to contend against other diseases. The Rockefeller Foundation has already done much. Some full time research workers are adding at intervals a few details of new information. But their number is small and their work must be supplemented by the regular physicians who can add many details from careful study of the patients in their own practice.

Hence the plea that I especially want to emphasize is that each medical man adopt the research attitude toward his cases and then give this society the benefit of his findings.

The specialist in pathology will always be needed, as is the specialist in all departments of medicine, but all physicians and all medical specialists will investigate more and more the pathologic side of medicine in the study of their patients and will be more and more interested in the added information that the special pathologists can give them.

October 8, 1923.

A CASE OF LEIOMYOMA OF THE STOMACH WITH FATAL TERMINATION

H. GIDEON WELLS

Department of Pathology, University of Chicago and the Otho S. A. Sprague Memorial Institute

Leiomyoma of the stomach is generally considered to be a rare tumor. If we include all the innocuous little myomatous nodules that may be found in the stomach wall, however, they are not extremely uncommon. In 1,000 necropsies I have observed five such tumors of varying size. One of these, however, is unique in that it contains a metastatic growth from a primary carcinoma in the lung.

Myomas of the stomach large enough and so located as to cause clinical manifestations, however, are extremely rare. Nadeau and MacCarthy,[1] Farr and Gleen,[2] Nassetti [3] and Kronjetzny [4] have reviewed the literature, Nassetti collecting 140 cases, in only four of which was an associated gastric ulcer described. Of these, 58 were simple myomas, 37 fibromyomas, 6 adenomyomas and 1 myxomyoma; all the others were described as mixed myosarcoma or malignant myomas.

Nadeau and MacCarthy say that during a period in which 1,194 cancers of the stomach were operated upon there were observed at operation 15 benign gastric tumors, of which 5 were leiomyomas, 3 fibromas, 2 fibromyomas and 1 adenoleiomyoma. These were all observed in operating on patients with pyloric stenosis with suspicion of malignancy. In 1922 a report from the Mayo Clinic by Eusterman and Senty [5] records 27 cases of benign tumor observed among 2,168 operated and 2,285 inoperable gastric neoplasms. These include 10 myomas (3 leiomyomas, 3 adenomyomas, 4 fibromyomas). Several were large enough to be palpated before operation, and in two there was gastric ulceration but not immediately over the tumor. Most of these tumors

1. Trans. Chicago Path. Soc. **10**: 51, 1916.
2. New York M. J. **97**: 1351, 1913.
3. Tumori, Rome **4**: 360, 1915.
4. Beitr. z. klin. Chir. **119**: 53, 1920.
5. Surg., Gynec. & Obst. **34**: 5, 1922.

were disclosed accidently in operating for other conditions. They were usually small growths, the largest being 5x7 cm.

Much larger growths have been described, however. Basch [6] mentions one removed by von Erlach which weighed 5,400 grams, one by von Eiselsberg the "size of a man's head," while more recently Kratzeisen [7] reported finding, in the body of a soldier who died of influenza, a fibromyoma weighing 5,000 gms. (including the stomach). This arose from the external surface near the pylorus with a pedicle 1 cm. long. Apparently there had been no clinical manifestations that were known. Kratzeisen refers to a tumor observed by Kaufmann which weighed 2,325 grams, to Spencer's case (200 grams) and cites other cases. Konjetzny reviews the literature and mentions that in 3,500 autopsies Tilger found but 14 fibrous or myomatous gastric tumors, of which there were 3 pure myomas, 3 fibromyomas, 2 lipomas and 7 pure fibromas.

Hunt [8] has found nine published cases since Nassetti's report, and adds one of his own, making a total of 150 benign and malignant gastric leiomyomas collected from the literature to 1923. Of these 10 new cases, at least 5 were malignant, making a total of 107 benign gastric leiomyomas. In his own case hematemesis was a conspicuous feature, leading to a diagnosis of duodenal ulcer. The tumor "about the size of a lemon" was removed by operation with recovery, but a year later there was a recurrent growth in the scar indicating that the tumor was malignant, although the histological diagnosis was leiomyoma.

As suggested above, most of these growths are symptomless, but sometimes they cause obstructive symptoms, or hemorrhage, leading to operation, as in the cases of Hunt,[8] Friedrich [9] and Cooper.[10] Hünermann [11] reports that between 1902 and 1922, 1,125 tumors of the stomach were observed at von Eiselsberg's clinic among which were 4 myomas. These

6. Surg., Gynec. & Obst. **22**: 165, 1916.
7. Ztschr. f. Krebsforsch. **19**: 227, 1922.
8. Boston M. & S. J. **188**: 349, 1923.
9. Deutsch. med. Wchnschr. **46**: 1139, 1920.
10. J. A. M. A. **80**: 349, 1923.
11. Arch. f. klin. Chir. **124**: 258, 1923.

myomas had in each case caused marked gastric symptoms with loss of weight. Operative removal of the myomas, which varied in size from "hen's egg to apple," led to prompt restoration of health. He also mentions that von Eiselsberg at one time observed a myofibroma weighing 5.5 kilos, in the stomach of a woman 30 years of age; this is probably the tumor mentioned by Basch,[11] and apparently is not included among the 4 cases reported by Hünermann. Mention may also be made of a gastric tumor reported by De Massary and Walser[12] which led to anemia, gastric symptoms, hematemesis and melena. The tumor, which was removed by operation, was reported by them as a glioma infiltrated by eosinophiles, but the description and illustrations of their case are not convincing that so improbable a diagnosis is correct.

In but few cases has the benign neoplasm been the cause of death. In that reported by Farr and Glenn, fatal hemorrhage occurred from the ulcerated surface of the growth, there having been no gastric symptoms previous to the fatal hemorrhage. In their compilation the only cases resulting fatally were those reported by Niemeyer and by Kernke in which the cause of death was hemorrhage, and a case reported by Pernice in which death was from pyloric obstruction.

In view of the evident infrequency of large gastric leiomyomas, and especially of fatal complications from such tumors, it seems desirable to place on record a case which was recently observed at the Cook County Hospital.

The subject as a white male, 33 years old, who entered the hospital Jan. 9, 1923, stating that he had been previously in the Washington Park Hospital, a patient of Dr. E. E. Tansy, who kindly gave me the following information: The man was a laborer, who first was taken ill about November 20 with symptoms resembling those of influenza, with vague chilling and pain in the thorax. About December 1 he began to complain of severe pains in the right knee, and on December 4 he was taken to the hospital. At this time he began to be troubled by severe hiccoughing which continued for about a week despite the use of morphin, papine and benzyl

12. Bull. Soc. Med. Hôp. **47**: 284, 1923.

benzoate. He had an irregular temperature, reaching 101 or slightly more nearly every day. Despite the hiccoughing, there were no gastric symptoms, he had a good appetite most of the time, and vomited but once in the hospital, the vomitus, however, containing black material. The presence of black stools was also noted at this time, but not after December 10. The urine was normal and the leukocyte count on December 6 was 11,100; on December 10 it was 14,800. The condition in the knee grew worse and on December 19 the joint was aspirated, pus being obtained in which neither tubercle bacilli nor gonococci could be found. The temperature remained elevated, the patient at times was irrational, on December 27 the knee was again aspirated. On December 29, a blood culture was negative. The Wassermann test of the blood was recorded as 1 + at this time. On January 9, he was sent to the Cook County Hospital, where the patient presented a septic condition, with abundant purulent discharge from the knee, in which drainage tubes had been inserted. For the last ten days before his death on January 24, he suffered from severe and persistent hiccoughs, which alarmed him greatly because, he said, his father and brother had each died after protracted hiccoughing attacks. While here, there were no gastric symptoms.

The clinical diagnosis was suppurative arthritis, sepsis and acute bronchitis. At no time had there been any indications of any gastric disease except the one attack of hematemesis and melena in December. The Wassermann reaction January 10 was negative.

The essential necropsy findings are indicated by the following anatomical diagnosis: Ulcerating leiomyoma of the stomach with abscess formation. Dense perigastric adhesions. Fibroma in pleura. Syphilitic hepatitis. Acute suppurative osteo-arthritis of the right knee with extensive suppurative cellulitis in the thigh and leg. Acute suppurative bronchitis. Hypertrophic pulmonary emphysema. Bilateral adhesive fibrous pleuritis. Multiple healed fibrous and calcified tubercles in the pleurae. Parenchymatous swelling of the kidneys. Acute splenic swelling. Adhesive right fibrous periorchitis. Marked emaciation. Tuberculous lymph node. Healing cutaneous wound in right axilla. Drainage wounds in right knee.

As to special findings, the body was greatly emaciated, and there were drainage wounds in the right knee joint. The joint cavity contained a bloody purulent fluid with blood clots in the periarticular tissue. The joint surfaces were gone, leaving eroded necrotic bone, the femur being more involved than the tibia. The necrosis, however, was very shallow,

2-3 mm., and involved also the articular surface of the patella. The necrosis of the muscles and fascia extended upward 15 cm. along the outer side of the femur, where the periosteum was intact, and in a sinus 15 cm. down the inside of the leg. All these sinuses were full of pus. No other bones and joints showed any lesions.

The liver was much lobed by deep scars. The parenchyma around these scars was infiltrated with connective tissue. The scars were radiating, and some caused puckering, a piece of the right lobe being almost pinched off to form an accessory lobe. There were many pinhead-sized yellowish spots which showed no discharge on compression, scattered through the liver. The gallbladder was normal.

A firm, light colored mass, 8 cm. in diameter, lay immediately behind the junction of the esophagus and stomach. It arose in the wall of the stomach and surrounded the posterior three-fourths of the esophageal opening without occluding it. It was bound by firm fibrous adhesions to the liver, diaphragm, tail of the pancreas and left adrenal. Opening the stomach, the mass was found to have an ulcerating surface in the mucosa, 3 cm. in diameter. Opening the tumor, this ulcer was found to communicate with an abscess, 4-5 cm. in diameter, lying in the tumor mass between the stomach and the liver. It was filled with a greenish pus which contained many streptococci. The tumor itself was lobulated, and firmly encapsulated, composed of a white tissue about the consistency of liver, divided up by connective tissue septa into vague lobules. Otherwise the stomach and intestines appeared normal. The lymph nodes about the tumor were slightly enlarged but not definitely involved by tumor tissue.

The pancreas was normal, but the tail was bound to the tumor mass around the stomach.

The left pleural cavity was normal, without adhesions, and the diaphragm was at the fifth interspace. The right pleural cavity contained dense fibrous adhesions over the posterior surface and base. There were several small hard nodules in these adhesions, one of which, 8x10 mm., was composed of dense fibrous tissue with a few calcified areas. The diaphragm was at the fifth rib.

In the lungs there was a severe diffuse suppurative bronchitis, but no pneumonic foci or abscesses.

Histology.—The gastric tumor is a pure leiomyoma, with very little of fibrous elements. The ulcerating surface shows bacterial thrombi extending deeply along the small vessels, surrounded by a zone of suppuration.

The liver shows typical healed syphilitic scars, although with much round cell infiltration in some places. There are

no microscopic changes corresponding to the focal discolorations seen in the cut surface.

The lungs exhibit marked suppurative bronchitis and atrophic emphysema.

In the spleen and kidney there are no marked changes.

The knee joint surface shows acute suppuration, with granulation tissue, and no evidence of tuberculosis.

An enlarged axillary gland shows fibrosis. A lymph node shows early miliary tuberculosis; its site is unknown, but it was not intrathoracic and probably it is one of the enlarged glands found near the stomach.

DISCUSSION

From the autopsy findings and the clinical record it seems probable that the suppurative arthritis and sepsis which caused the death of this subject, were secondary to infection of the ulcerated gastric tumor. The extent of ulceration and suppuration in the tumor indicate that this was the source of the infection, which is supported by the presence in the tumor of numerous septic thrombi filled with bacteria. Furthermore, no other apparent source of the infection could be found. It seems probable also that the acute inflammatory swelling of the tumor, located in immediate contact with the diaphragm, accounts for the severe and persistent hiccoughing. One wonders as to the possible cause of the fatal hiccoughing attacks of the father and brother of the patient, if his statement is correct as to this family history.

October 8, 1923.

TESTICLE REINFECTION IN EXPERIMENTAL TUBERCULOSIS, AND THE TESTICLE TUBERCULIN REACTION

ESMOND R. LONG

The testicle can be used as an indicator of the hypersensitive state in tuberculosis. The testicle of the tuberculous animal is exceedingly sensitive to tuberculin, and displays a characteristic resistance to reinfection. An essential feature of this resistance is the pronounced testicle tuberculin reaction, manifested in the first few hours after the reinfection.

The testicle test is at least as delicate as the skin test, and much more accurately controlled when used in the manner which I shall outline. It offers a means of detecting tuberculin in high dilution, as for example in urine or in the bodies of other bacteria than the tubercle bacillus.

In making the test male guinea pigs of about 500 gms. weight are used in two pairs, each pair consisting of one normal animal and one with a mild axillary gland tuberculosis of about one month's standing. The two pairs are inoculated directly in the left testicle with 0.1 cc. Old Tuberculin 10 times diluted, or with the unknown material in case tuberculin is being sought. One pair is killed at the end of 48 hours, the other at the end of one month. The picture at the end of these two periods I call the early and late tuberculin reactions respectively.

The chief manifestations of the early tuberculin reaction are grossly a marked hyperemia of both testicle and tunica with great swelling, and microscopically intertubular edema, wandering cell infiltration, and degeneration with beginning necrosis of the spermatocytes and spermatids.

The chief manifestations of the late tuberculin reaction are profound atrophy of the germinal elements, with interstitial wandering cell persistence and an extraordinary hyperplasia of the interstitial cells of Leydig; the tubules remain, perfectly outlined by undifferentiated epithelial cells upon an intact basement membrane, but spermatocytes, spermatids and spermatozoa have disappeared. Complete sterilization has been effected.

Upon the testicle of the normal guinea pig tuberculin has no effect, either early or late.

There is a profound difference in the response of the testicle to tubercle bacillus infection in normal animals and animals already infected with tuberculosis. The guinea pigs with a light axillary infection respond in 24 hours with marked hyperemia and swelling of the testicle. Microscopically extraordinary degeneration or even coagulation necrosis of the germ cells is observed, together with intense epithelioid cell infiltration. At this period the testicle of the previously non-infected

guinea pig shows practically no gross abnormalities, and microscopically only a moderate wandering cell infiltration.

After a time the tuberculosis of the pigs not previously infected tends to catch up with that of the previously infected animals. Three or four weeks after the testicular infection the testicles of the two groups may show no great differences. There is, however, a rather general tendency on the part of the previously infected pigs to supplement the epithelioid cell reaction with the proliferation of fibroblasts and to limit the new infection to the testicle, and a tendency on the part of the guinea pigs never before infected to suffer caseation necrosis of the infected testicle and marked extension to other organs. A noticeable feature in the reinfected pigs, which distinguishes the microscopic picture, is the slow absorption of the tubules which have undergone coagulation necrosis.

After six weeks there is usually a well defined difference. The testicle of the previously infected animal is small, rich in epithelioid cells and moderately rich in fibroblasts. There is little necrosis. Corresponding to the abundant proliferation of epithelioid cells there is a marked deposition of reticulin, as shown by the staining method of W. S. Miller. In the other group, where the testicle infection was primary, the testicle is also small, but soft and largely necrotic. Microscopically only a moderate epithelioid cell infiltration is seen, corresponding with which there is only moderate deposition of reticulin. Fibroblast proliferation is slight.

The testicle tuberculin test here described is highly characteristic of the "hypersensitiveness of infection." It is not an anaphylactic response. Guinea pigs sensitized with proteins, as egg albumin and gliadin, do not give a testicle reaction on intratesticular injection of these proteins three weeks later. Neither after two days nor one month is any effect upon the testicle to be noted. On the other hand an abortin testicle test of identical type can be obtained on injection of abortin into the testicle of guinea pigs with Bacillus abortus infection.

November 12, 1923.

THE RÔLE OF THE LIVER IN MAINTAINING THE NORMAL SUGAR CONCENTRATION OF THE BLOOD

S. A. MATTHEWS
Loyola University School of Medicine, Chicago

One of the favorite methods used to determine the function of an organ that has to do with the metabolism of the body is to extirpate or otherwise destroy the organ, and if its destruction is compatible with the life of the animal, to determine the metabolic processes uninfluenced by the organ. This method has been extensively applied in the study of the functions of the liver, and has resulted in important findings. Eck (1877) was the first to shunt the liver out of the portal circulation. This he did by means of a fistulous opening between the portal vein and the inferior vena cava (Eck-fistula) and then tied off the portal vein. He used ducks and geese in his work because the peculiar circulation in birds made the operation comparatively easy. By means of this operation which has been applied to mammals, subsequent investigators have been able to remove the liver altogether.

All investigators agree that the lease on life after extirpation of the liver is but a few hours, eight to twelve at most, and that as a general rule the animals die in coma. One of the things observed by former investigators, namely, Minkowski,[1] Kausch,[2] Diamare,[3] Pavy and Siau,[4] and Kaufmann[5] using frogs, ducks, geese and dogs was that the glucose practically disappeared from the blood after extirpation of the liver, and that hyperglycemia and glycosura did not develop in pancreatiectomized ducks and geese (Kausch[2]). More recently Mann[6] has corroborated these previous findings, using dogs, and has conclusively shown that the

1. Minkowski, O.: Arch. f. exper. Path. u. Pharmakol. **21**: 41, 1886.
2. Kausch, W.: Arch. f. exper. Path. u. Pharmakol. **39**: 219, 1887.
3. Diamare: Arch. ital. biol., 1912 (Chem. Abstracts, 1912) **6**: p. 1634.
4. Pavy and Siau: J. Physiol. **29**: 375, 1903.
5. Kaufmann: Arch. de physiol. norm. et path. **8**: 767, 1896, 5th series.
6. Mann: Am. J. Physiol. **55**: 285, 1921. Mayo Clinic, 1922, p. 125. Am. J. Physiol. **65**: 403, 1923.

removal of the liver is followed in from six to ten hours by a drop in the blood sugar to 0.03 per cent. or lower. At this low level his animals passed into a comatose condition, sometimes convulsions intervening, and soon died. He has also shown that all these symptoms are quickly counteracted by the administration of glucose and the life of the animal prolonged for several hours longer.

Since the advent of insulin, the administration of which brings about a great reduction in the blood sugar in the space of a few hours, and is followed by intense poisoning and death, with symptoms similar to the symptoms following extirpation of the liver, both of which are relieved by the administration of sugar, it is quite tempting at least to attribute the intoxication in both cases in terms of blood sugar reduction. This is paramount to saying that the blood sugar cannot be reduced below 0.04 per cent. with safety to an animal, and that it is one of the functions of the liver to maintain the sugar constant of the blood at about 0.08 to 00.1 per cent.

Studies on the blood sugar in cirrhosis and in the various clinical degenerations of the liver, as well as the effects of destruction of the liver by chemicals have given rise to contradictory results, but with a tendency towards a hypoglycemia. In Eck-fistula dogs, especially those that are made subjects of meat intoxication by operation, the liver gradually degenerates so that at the end of two years the parenchyma is almost completely atrophic. Such animals are generally hypoglycemic to a marked degree, often showing a blood sugar as low as 0.03 per cent., yet if properly fed, may enjoy good health. The glycogen in both the liver and muscle is much diminished. This condition suggests, at least, that it is possible for an animal to become more or less immune to the effects of a low blood sugar, when the conditions favoring a diminution of the blood sugar is slowly developed—in these cases by a slow degeneration of the liver.

Eck-fistula dogs, subject to meat intoxication, generally show a low sugar tolerance, and glycosuria may be present on an ordinary diet. This indicates that the

poisons absorbed from the intestines exert a phlorizin-like action upon the kidneys and may be one of the factors involved in the hypoglycemia. The poisons formed in the intestines from protein digestion, the action of which is made manifest by an Eck-fistula, also exert their action upon the central nervous system. In acute intoxication the syndrome is that of incoordination similar to cerebellar poisoning. In chromic poisoning the syndrome is also nervous in which there is a progressive breakdown of the proprioceptive function of the central nervous system. The exteroceptive function and all the somesthetic sensibilities remain unimpaired. In fact, one animal so affected showed the classical symptoms of cerebellar extirpation. Dr. G. B. Hassin of Cook County Hospital carefully determined the pathology of the central nervous system of this dog and found marked degeneration of the spinal cord somewhat resembling multiple sclerosis. The sclerosis involved the anterior, posterior, and lateral columns of the cord, leaving the gray matter untouched. The molicular layer of the cerebellum was markedly infiltrated with glia cells. The pathology found in this case showed very clearly the paths in the spinal cord involved in the maintenance of the proprioceptive function.

November 12, 1923.

THE EFFECTS OF THE SHORT WAVE LENGTH ROENTGEN RAYS AND DIATHERMY ON TRANSPLANTABLE RAT CARCINOMA

(PRELIMINARY REPORT)

BERNARD PORTIS

From the Snyedacker Fund of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research

The advent of the short wave length roentgen therapy has stimulated renewed interest in the use of this agent in the treatment of cancer. The literature is now very extensive with clinical results, many of which are highly

favorable, while others conclude that short wave length roentgen rays have only a slightly increased beneficial local effect and frequently produce severe generalized reactions. Diathermy also, is being used to greater advantage and many have combined this agent with the new roentgen therapy with very satisfactory results. However, there still remains a great paucity of reports on the effects of these two agents on transplantable tumors in animals.

LITERATURE REVIEW

Roentgen rays have been used in the treatment of malignancy since their discovery, but this therapeutic measure has received a great impetus through the discovery and perfection of the apparatuses capable of delivering 200,000 volts of electricity. The introduction of the Coolidge tube has made possible the use of such quantities of deep penetrating rays over any extended period. Wood [1] has stated that the new apparatus yields about 40 per cent. more voltage, and with this increase the roentgen rays approximate the electromotive force of radium. The measurements of radiations applied to any tissue have been estimated by many different instruments. The electroscope is very accurate for radium and its emanations. The determination of the roentgen ray dosage has been more difficult. Various arbitrary dosages have been suggested, but the chief methods utilized now are the erythema dose, estimation of the "e" units, and the use of an electroscope in conjunction with ionization chambers.

Ewing [2] has stated that there are more distinct clinical and pathological entities within the groups of neoplasms than exist outside of them. This complexity of structure of new growths is associated with variations in the reactions to roentgen therapy. Bergondie and Tribondeau expressed the sensitivity of tumor tissue to roentgen rays as a law, which stated that immature cells and cells in an active state of division are more sensitive to roentgen rays than those cells which have already acquired their adult morphological characteristics.

1. Wood: Med. Rec. **101**: 399, 1922.
2. Ewing: J. Cancer Res. **1**: 71, 1916.

Webster stated that the reaction induced in cells was similar for all types, differing in degree with the quantity of radiation absorbed. L. Loeb [3] found that malignant tumors were especially vulnerable to radiation because of their rapidity of division, and the immaturity of the cells. Many authors have considered a small dose of radiation as stimulatory, but they cite neither conclusive proof nor plausible explanation for this assumption.

The physical and chemical effects of radiation seem to depend on the ionization produced by the roentgen rays (Nakahara and Murphy [4]). Neuberg [5] has shown that radiation destroys all the enzymes which carry on the metabolism of the cells, but does not injure the autolytic enzymes, thus allowing the latter to be active after the destruction of the vital processes in the tissue exposed. Webster [6] believes that the increased lipoid content of the immature cells makes them more susceptible to radiation.

Alter [7] demonstrated that radiation will accelerate differentiation in immature epithelial cells, and decrease growth in mature cells. Ewing [8] considers that tumor tissue is never killed directly, as the result of radiation, but believes that the necrosis which does occur results from the failure in the circulation caused by the occlusion of delicate vessels, leading to anemic infarction. He also considers the state of the tissues immediately adjacent to the tumor of great importance. The changes usually noted are capillary proliferation, and leucocytic, lymphocytic and plasma cell infiltration. Opitz [9] was able to demonstrate the presence of vitally stained mononuclear cells, often histiocytes, in large numbers about experimental tumors subsequent to radiation.

Nagel Schmidt and Doyen were the first to use the high frequency current for coagulation of tumor tissues.

3. Loeb: Am. J. Roentgen. **9**: 502, 1922.
4. Nakahara and Murphy: J. Exper. M. **35**: 475, 1922.
5. Neuberg: Ztschr. f. Krebsforsch. **2**: 171, 1904.
6. Webster: Arch. Radiol & Electroth. **258**: 244, 1922.
7. Alter: J. M. Res. **41**: 439, 1920.
8. Ewing: Am. J. Roentgenol. **9**: 331, 1922.
9. Opitz: Ibid. **10**: 312, 1923.

Iredell and Turner [10] consider the effects of this form of therapy to be dependent upon the production of heat in the tissues caused by the resistance offered the passage of the high frequency current. Rhodenburg and Prime [11] lay especial emphasis on the size of the two electrodes. This diathermic agent is produced by an instrument furnishing d'Arsonval current of 1000-2000 milliamperes. Stevenson,[12] as the result of his own observations, determined that all tumors are killed when exposed to temperature of 47-48.5°, for 15 minutes, and that carcinomas were somewhat more resistant to temperature changes.

The combined use of roentgen rays and diathermy was first employed by de Keating Hart who also was one of the first to use the diathermy current for clinical purposes. Schmidt [13] advanced the theory that heat sensitizes the tissue to radiation. Rhodenburg and Prime [11] found that sublethal doses of radiation and diathermy produced the same effects as four times the dose of diathermy alone and five times that of radiation exposure alone when acting upon tumors in vitro. They also observed similar effects in vivo. Kolischer and Katz [14] found that surgical diathermy was a potent factor in enhancing the efficiency of radiotherapy in the treatment of bladder tumors. Many have used this combined method in the treatment of malignancies about the mouth and nose.

EXPERIMENTAL

The tumor used for this experimental work was received from the Crocker Institute for Cancer Research through the kindness of Dr. Francis C. Wood. It was a transplant from the original Flexner-Jobling rat carcinoma discovered by these individuals in a male rat which died spontaneously on January 5th, 1906. There were no metastatic growths in the original animal, but during its later transplants, the tumor has become a very characteristic malignant growth. Histologically,

10. Iredell and Turner: Proc. Roy. Soc. M. **12**: 23, 1919.
11. Rhodenburg and Prime: Arch. Surg. **2**: 116, 1921.
12. Stevenson: J. Cancer Res. **4**: 54, 1919.
13. Schmidt: Fortschr. a. d. Geb. d. Röntgenstrahlen **14**: 135, 1909.
14. Kolischer and Katz: J. Radiol. **4**: 76, 1923.

the tumor consisted of a simple tissue with an imperfectly organized structure and numerous glandular elements. Later it lost its glandular character and had become transformed into a solid, cellular, alveolar carcinoma.

The tumor had been found to be in the most active state of growth for transplantation at the end of two weeks. Young rats about 2 months of age are most susceptible. Small fragments of the tumor are removed from the larger growths and are inserted by means of a trocar into the subcutaneous tissues in the interscapular regions. These transplants are allowed to grow for a period of three to four weeks; by this time they usually produce a growth about 1x1x2 cm.

The earliest work concerned the development of a standard roentgen ray dose. Attempts were made to determine the erythema dose. The physical experimental side of this problem was accurately controlled by Mr. H. N. Beets, a physicist from the University of Chicago and research fellow in radiology at the Michael Reese Hospital. The "e" unit of roentgen ray quantity is defined by Kronig and Friedrich as that quantity of radiation which transports one electrostatic unit of electricity, with a saturated current, in 1 cc. of air under normal conditions. It is measured by an ionization chamber and electroscope, both of whose electrical constants are known. It was found that the human skin shows a definite erythema when exposed to 1,800 "e" units.

A series of adult rats were exposed to roentgen rays in order to determine the erythema dose. They were attached to a specially designed board and shielded with sheet lead 5 mm. thick so that only about 4 square centimeters in the interscapular region were exposed to the radiations. The skin target distance was 38 cm.; voltage, 200,000; milliamperes, 6; and filter of 0.5 mm. of copper. The length of exposure varied from 20 to 120 minutes. Blood counts were made every day for several weeks. There were no consistent changes in either the total red or white cells counts. The differential counts showed a marked reduction in the circulating lymphocytes and the duration of this decrease varied directly

with time of exposure. A stimulatory response was only noted in one rat which had received a 20 minute exposure. The erythema dose was recognized by the appearance of alopecia and later of a superficial dermatitis which persisted for about two weeks and left a scaling lesion. It was found that the rats needed to be exposed for 120 minutes in order to produce the desired reaction; this dose corresponded to 3,400 "e" units.

Several rats, with tumors about 4 weeks old, were exposed to this standard dose. They were then injected with 2 cc. of 1 per cent. trypan blue in order to vitally stain them. They were killed at the end of 24 hours. The tumors and the adjacent tissues were removed, fixed in 10 per cent. formaldehyde and frozen sections were made. They were stained with alum carmine solution and picric acid. Other tumor containing rats, without any previous exposure to the roentgen rays, were subject to the same technic. These preparations yielded characteristic pictures. The trypan blue was found to distribute throughout the entire body, but in reference to the tumor it was noted that the tissues immediately adjacent to the growth had taken on a more intense vital stain, this occurring in the tissue macrophages. Rats that had had a previous roentgen exposure had a more intense and more extensive reaction zone about the tumors.

A number of well advanced tumor growths were treated with the standard exposure and then observed over a period of several weeks. In all of the rats containing a tumor over 2 cm. in diameter death occurred in from 3-7 days, being earlier in those animals with the larger tumors. The histological findings in these animals revealed an extensive necrotising process, the only viable cells being seen in the periphery of the growth, and even here the nuclei were intensely pycnotic. The vessels about the tumor were free from thrombosis or obliteration. This early fatal result seemed to be due to the overwhelming of the animal by the autolytic products of the exposed tumors. Rats with smaller tumors lived for many weeks and the only noticeable changes were those of a steady decrease in the size and practically total destruction of the tumor

tissue, with some absorption. These rats seemed to be predisposed to the development of pneumonia following exposure over the thoracic regions.

The standardization of the diathermic dose was a very difficult matter. Preliminary experiments with raw beef showed that with a current of 1,100 milliamperes, 5.0 cm. electrode and a thirty second exposure, there resulted complete coagulation for a depth of 5 mm. and the temperature increased up to about 60°. However, even though this appeared as the most satisfactory combination, it could not be used unchanged because the tumors were covered with skin, which offered considerable resistance to passage of the current.

This diathermic current was applied to several rat tumors; the animals were vitally stained with trypan blue and studied in a similar manner as those which had received the exposure to the roentgen rays. Sections of these tumors showed a similar increase of vital staining in the reaction zone about the tumor. Hyperemia was present in this region and the trypan blue appeared to be chiefly in the macrophages, which were increased in numbers and were more deeply stained than was the case in untreated control animals. The advanced tumors treated with the diathermic current did not show the early fatal results observed after the roentgen exposure.

A number of rats were exposed to radiation and diathermy, alternating the order of application of these agents. This reaction is now under consideration but the preliminary results indicate an increased efficiency of the combination and several otherwise supposedly fatal roentgen exposures were not followed by death when diathermy was used subsequent to radiation.

SUMMARY

The rat skin is more resistant to roentgen rays than human skin. It requires about twice the length of exposure to produce comparable reactions.

The changes in the circulating lymphocytes produced by the exposure correspond to those observed by many workers, notably Murphy and his collaborators.

The increased vitally stained reaction zone about the tumor may indicate that roentgen and diathermy rays have a stimulative reaction on the normal protective processes of the body or that they produce changes in the tumor tissue which stimulate the phagocytic activity of the adjacent tissues.

The short wave-length roentgen rays are very effective in producing lethal effects on the rat carcinoma. A widespread and often complete necrosis of the larger tumors, however, causes toxic reaction in the animals and often death. This may be due to the destruction of the oxidizing enzymes without an inhibitory action on the autolytic enzymes, a finding observed by Neuberg.

Diathermy also has a marked destructive action on the transplantable tumors. An equal destruction of tumor tissue by this agent is not followed by the toxic death of the animal so frequently as is the case after roentgen ray exposure alone. This may be due to a destruction of the autolyzing as well as the oxidizing enzymes by the diathermic current.

The combined use of the short wave length roentgen rays and diathermy seems to be more effective than either alone.

November 12, 1923.

THE PREPARATION OF DRY POWDERS WITH SPECIFIC IMMUNE PROPERTIES

EDWIN F. HIRSCH

From the Pathological Laboratory, St. Luke's Hospital, Chicago, Ill.
Aided by the Winfield Peck Memorial Fund

The preparation of solids with immune properties has been limited to the direct evaporation of immune serums. Soon after antitoxin became important in the treatment of diphtheria, antitoxin powders were made by Rosenau. These were kept dry with phosphorus pentoxide in suitable glass containers. Similar preparations of immune serums and complement serums have been made by others, recently by Hartley, Eagle-

ton and Okell. No attempt at purification is made with these preparations.

It is known generally that the substances with immune properties are carried in the globulin fraction of serums, either in the true globulins, or in the pseudo-globulins. This has been shown especially well by Pick's classic experiments. Practical methods for concentrating immune substances from serum depend largely upon salting out with a globulin precipitant such as ammonium or magnesium sulphate. The last mentioned being least satisfactory, generally speaking.

Commercially the importance of concentrating and refining antitoxins, such as against diphtheria and tetanus, has prompted various methods. The first practical method was suggested by Gibson. He found the antitoxin contained in the pseudo-globulin fraction of horse serum and accordingly precipitated the globulin from horse serum by half saturating with ammonium sulphate and then after washing, dissolved out the pseudoglobulin with a saturated sodium chlorid solution. From the saturated salt solution the antitoxin is precipitated with acetic acid or by half saturation with ammonium sulphate. The precipitate obtained with acid is dialyzed, neutralized with sodium carbonate, and sterilized; that obtained by second precipitation with ammonium sulphate is dialyzed, and then sterilized. Other methods have been suggested by Banzhaf, and more recently by Heineman, these depending upon fractional precipitation of the globulins with ammonium sulphate, combined with heating to certain temperatures of the precipitating mixtures. These refining methods concern the concentration of antitoxins for commercial purposes.

Certain studies with precipitin serums suggested the possibility of concentrating the precipitins in the hope of affording better opportunity to study the chemical behavior of these substances. Precipitins were found to be contained largely in the euglobulin fraction of rabbit serum. In discussing these observations with Dr. E. R. LeCount he suggested the possibility of reducing to solid form the substances in solution responsible for the precipitin reaction.

The precipitation of globulin from serum by dilute acids has been known for some time. According to Dieudonne and others this portion contains no substance with immune properties. In experiments with the hydrogen-ion range of the precipitin reaction this globulin fraction was precipitated from sheep serum, washed thoroughly with distilled water, and dissolved in water alkalinized with a few drops of N/100 NaOH. This globulin solution reacts with homologous immune serum within a hydrogen-ion range the same as that observed for mixtures of native serum and immune serum. It seems then that this portion may be removed without loss of the immune substances, excepting as these are occluded mechanically in the precipitate.

Accordingly the method developed, based on observations already mentioned, in principle, is as follows:

Immune serum is brought slowly to *p*H 6.8 with N/100 HNO_3 usually 1 to 3 cc. per cc. of serum, the larger volume when blood is citrated. At about *p*H 6.8 a fibrin clot forms or flocculation occurs. After standing in a cool place until flocculation is complete the liquid is filtered and to the clear filtrate, more N/100 HNO_3 acid is added until a maximum turbidity is obtained. This upon flocculating is removed by filtering and the clear filtrate is half-saturated with ammonium sulphate. The precipitate is washed thoroughly with a half-saturated aqueous solution of ammonium sulphate. From this stage on the method varies depending upon which globulin fraction contains the substance with immune properties.

For euglobulin. Precipitins, agglutinins, amboceptor (rabbit serum).

The precipitate on the filter is washed thoroughly with a saturated sodium chlorid solution to remove the pseudoglobulin. The precipitate remaining on the filter is dissolved in a volume of water about twice that of the original serum. To this liquid in the presence of a little salt N/10 HC_1 is added drop by drop. A white flocculent precipitate settles out, more forms upon standing.

For pseudoglobulin. Diphtheria antitoxin (horse serum).

The pseudoglobulin is precipitated from the saturated sodium chloride solution with ammonium sulphate, the precipitate collected on filters, dissolved in a volume of water equal to twice that of the original serum and then precipitated by adding N/10 HC_1 and a small volume of saturated sodium chloride solution.

The precipitates obtained by either method are collected by centrifuging and then dried in a vacuum dessicator. During the drying most of the dissolved salt creeps out. When thoroughly dried the substances may be reduced to a white powder in a mortar.

The powdered substances are soluble in water, giving an acid reaction to the liquid, more readily in water with a little N/10 or N/100 NaOH. When dissolved in water and then neutralized gradually with NaOH there is a certain reaction where the dissolved substance manifests the flocculation phenomenon. This is known as its isoelectric point, a reaction at which it is ionized equally as acid and as base. At this point its solubility is least. These reactions point to the preparations being protein-acid salts, such as a protein-hydrochloride. Experiments with the precipitin test have revealed a p_H range within which precipitation takes place. The protein salt probably dissociates like other ampholytes in a way such as Levene and Simms pointed out recently. Within a certain hydrogen-ion range where the basic dissociation predominates it combines with acid-substances to form acid salts, above and below this p_H range the basic dissociation is suppressed. Similar relations probably exist for antigenic substances, and the mutual concurrence of optimum relationship for both the antigen and the immune substance in a certain hydrogen-ion range, permits completion of the chemical phenomena characterizing an immune reaction. In discussing the isoelectric range of an ampholyte Levene and Simms say that with aspartic acid, glutanic acid, and many proteins the isoelectric point may be a sharp boundary marking a definite change in chemical behavior because of the proximity of the acid and basic dissociation constant to the isoelectric point.

A complete report will be made in several articles published in the *Journal of Infectious Diseases*.

December 10, 1923.

SUDDEN DEATH FROM SPONTANEOUS BILATERAL HEMORRHAGE IN THE SUPRARENAL GLANDS

REPORT OF TWO CASES

S. M. CROWE

From the Pathological Laboratory of Rush Medical College

Hemorrhage in the suprarenal glands causing death is rare in adults. In infants its greater frequency, according to Kempf,[1] is largely due to the organs being incompletely developed, highly vascular, and subject to venous stasis. Gunson[2] has reported infection of the umbilical stump with suprarenal hemorrhage. The trauma of labor and resuscitation is an added factor.

Trauma, however, in adults plays a small part. In his exhaustive discussion of the subject, Lavenson[3] considers the following causes of spontaneous suprarenal hemorrhage in adults: long-continued passive congestion of the organs, as in chronic heart and lung diseases; sudden increase in blood pressure, as in epilepsy and pertussis; hemorrhagic tendency in asphyxia; active congestion of the suprarenals; infections; severe surface burns; suppurative changes in adjacent organs. Thrombosis of the suprarenal veins has been reported frequently, either marantic (Simmonds, cited by Kempf[1]), or infectious. In many infectious diseases minute emboli lodge in the capillaries of the suprarenal glands as they do in other places. Hyperadrenia, a condition of hyperactivity of the suprarenal glands, according to Sajous,[4] may cause hemorrhage by increasing the blood pressure. Abnormal conditions of the blood, as leukemia and the hemorrhagic diathesis, have been considered factors by Kaufman[5] and Barker.[6] Attempts to demonstrate

1. Kempf, H.: Ueber die Bedeutung der Nebennierenblutungen für den plotzlichen Tod, Vrtljschr. f. gerichtl. Med. **56**: 71-96, 1918.
2. Gunson, E. B.: Suprarenal Hemorrhage in an Infant, Proc. Roy. Soc. Med., London, Section Study Dis. Child. **8**: 54,1914-15.
3. Lavenson, R. S.: Acute Insufficiency of the Suprarenals, Arch. Int Med. **2**: 62-73, 1908.
4. Sajous, I. T. deM.: Practice of Medicine, Tice **8**: 159-162, 1922.
5. Kaufman, Eduard: Lehrbuch der Speziellen Pathologischen Anatomie, 1911, 799.
6. Barker, L. F.: Nelson Loose-Leaf Living Medicine **3**: 222-228, 1921.

changes in the sympathetic ganglia, as suggested by Kempf [1] and others, have been unsuccessful in several instances.

Spontaneous hemorrhage in the suprarenal glands may be unilateral or bilateral, and may even cause rupture of the capsule. Thrombi in the veins may be visible grossly or just mural necrosis microscopically. Bacteria have been demonstrated in these lesions. The damage to the suprarenal tissue may vary from almost complete destruction to compression of the cells with only a little necrosis. The medulla is said to be more affected than the cortex usually. The alterations found in other organs post mortem are largely those of the condition responsible for the hemorrhage.

Clinically, Lavenson [3] recognizes five groups of symptoms: a peritoneal type with sudden onset of epigastric pain and vomiting; an asthenic type; a nervous type with convulsions, delirium, or coma; a group with a purpuric rash or hemorrhages in the abdominal organs; and lastly, those with sudden death. Usually the symptoms are considered those of acute insufficiency of the suprarenal glands. Commonly in addition to the symptoms of the primary condition, as infection, there are extreme muscular weakness, rapid pulse of poor quality, subnormal temperature, a variable amount of pain, and more or less vomiting and diarrhoea. Symmetrical erythema was reported by Lusk and Brumbaugh [7] in a young man with septicemia following the lancing of a felon.

Acute suprarenal hemorrhage, diagnosed, according to Severn,[8] rarely if ever before death, should perhaps be considered a possible explanation of acute prostration with low blood pressure, in the absence of evidence of other cause, as hemorrhage elsewhere. The presence of a palpable mass in the suprarenal region may be of diagnostic aid.

Extensive bilateral hemorrhage into the suprarenal glands is always fatal, and less extensive hemorrhage, even when unilateral, may be fatal.

7. Lusk, F. B., and Brumbaugh, A.: Nontraumatic Hemorrhage of the Suprarenal, J. A. M. A. **72**: 1062-1064, 1919.
8. Severn, A. G. M.: A case of Acute Bilateral Suprarenal Hemorrhage, Lancet **1**: 647-648, 1923.

Case 1.—J. W., an American teamster, 35 years old, was admitted in coma to the service of Dr. C. S. Williamson, at the Cook County Hospital, at 6:30 p. m., Aug. 13, 1923. From his wife it was learned that he was a heavy drinker, and had been in poor health and unable to work for the last six months, though not in bed. For the last year, he had complained of pain in the epigastrium, vomiting, a cough, and occasional night sweats. This day he had vomited repeatedly, supposedly because of drinking to excess the day before. When arising from a chair, shortly after 5:30 p. m., he had fallen to the floor with "cramps." On admission to the hospital, there were marked cyanosis, shallow, irregular, gasping respirations, 30 a minute; froth on the lips; loud, harsh breath sounds all over the chest; no apparent abdominal tenderness or rigidity; rapid, irregular pulse; discharge from the penis. At 7 p. m., the rectal temperature was 99° F., respirations 32 a minute, and the pulse imperceptible. The clinical diagnosis made by the intern was chronic alcoholism, probable gonorrheal urethritis, and possible pulmonary embolism. Administration of stimulants and oxygen was of no avail, and death occurred fifty minutes after admission to the hospital, less than two hours after the onset of acute symptoms.

At the postmortem examination, twelve hours later (Dr. E. R. LeCount), there were found: infarcted suprarenal glands; generally engorged cutaneous capillaries; focal punctiform hemorrhages in the leptomeninges of the frontal lobes of the cerebrum; hemorrhage in the choroid plexus; hypostatic hyperemia of the lungs; moderate mucopurulent bronchitis; marked chronic lacunar tonsillitis; acute catarrhal blepharitis, conjunctivitis, and laryngitis; diminished lipoid content of the suprarenal cortices; extensive fatty changes of the liver; cloduy swelling of the kidneys; and opacities of the leptomeninges of the cerebral cortex.

The skin was rose-pink, except where pressure had been. Some of the teeth were carious. The left suprarenal gland was plump and dark red, with practically no yellow on surfaces made by cutting it through the middle. It weighed 12.47 g., the right 16.65. The parenchyma of each was under pressure and, if anything, there was more blood in the substance of the right.

In the stomach content and portions of the liver and kidneys examined chemically, no volatile poisons, heavy metals, or alkaloids were found (Dr. William D. McNally, Coroner's Chemist).

On further examination, the formalin hardened right suprarenal gland is 68 by 50 by 12 mm. in maximum dimensions,

the left 56 by 35 by 15. The small amount of fat adherent to each is practically free from hemorrhage, except at the center of the front edge of the left, where it is quite brown for 12 by 9 mm. The right is dark blue-gray outside, with the normal yellow of the cortex only at the edges, and where the cortex is roughened by small elevations, up to 1 mm. in diameter, not over one-twentieth at most. On surfaces made by sectioning in the greatest dimension, the cortex is from 1.5 to 3 mm. thick, and the medulla is quite scanty, except at the hilum, where it is up to 2 mm. thick, light gray, and firm. The yellow of the cortex is mostly in narrow parallel streaks, amounting to about one-tenth of surfaces made per-

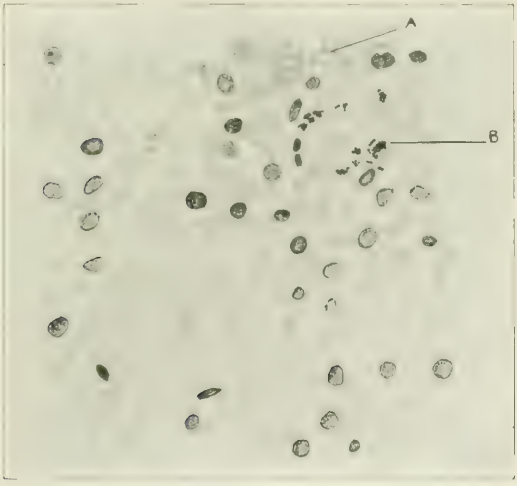


Fig. 1.—Drawing of a portion of the suprarenal cortex, high power, with the hemorrhage (*a*) and clumps of bacteria and fibrin (*b*), in the wall of a small vein (hematoxylin and eosin stain).

pendicular to the external surface. The outside of the left suprarenal gland is about one-sixth pale yellow. The medulla, on surfaces made by cutting, is visible only at the hilum, and is even narrower than in the right. The cortex is from 1 to 2 mm. thick, and is yellow about one-sixth. The lining of the attached portion of the vein of each gland is smooth and clean, of the left 15 mm., of the right 8.

In sections of the right suprarenal gland stained with hematoxylin and eosin, the cell columns of the cortex are

all crowded and compressed more or less by extravasated red blood cells, especially in the glomerular and fasciculate zones. The veins of the medulla are distended with blood, but where the medulla is recognizable, there is only a little extravasated blood, and that close to the cortex. There are, however, many groups of a dozen or more lymphocytes in the medulla. In many of the medium-sized veins are clumps of bacteria, in the lumens and in the vessel walls (Figure 1), and the continuity of the endothelium in places is broken. Collections of fibrin here are stained purple with phosphotungstic acid. More bacteria are present in the capillaries of the cortex.

In sections of the lung, there is only hyperemia and edema, of the liver marked fatty change, and of the spleen, no noteworthy alteration.

In sections of the right suprarenal gland, stained with Sudan III, there is about half of the normal amount of fat in the cortex (Figure 2). In sections stained for bacteria, there are Gram positive cocci in small groups and chains, in the veins and in the capillaries.

Case 2 (reported by the courtesy of Dr. Edwin F. Hirsch). —O. M., 30 years old, a Dane, had been well until the afternoon of Dec. 31, 1917, when he had a severe chill and went to bed. From midnight until morning, he had almost continuous bowel movements. He had no severe pain, and did not vomit. He had taken no medicine or unusual food. He was conscious when admitted to the hospital, at 11:35 the following morning, and there were: labored breathing; imperceptible radial pulse; cold face and extremities; deep cyanosis of the face, hands, and feet; many purpuric spots, pea to dime-sized, on the forehead, neck, and extremities. He died less than an hour and a half after entering the hospital.

In the postmortem examination (Dr. Hirsch), the same day, were found: extensive hemorrhage into both suprarenal glands; multiple petechial hemorrhages and ecchymoses of the tissues generally; acute left follicular tonsillitis; acute catarrhal laryngitis, tracheitis, and bronchitis; acute hyperplasia of the cervical lymph glands; icterus; slight serofibrinous pericarditis; cloudy swelling of the parenchymatous organs; hyperplasia of the spleen and mesenteric and biliary lymph glands; passive hyperemia of the tissues generally.

The skin of the face was mottled reddish, and was distinctly icteric, the lips were cyanotic, and the lower extremities purple. There were petechial hemorrhages of the conjunctivae and skin of the shoulders and arms, and larger hemorrhages, the size of the little fingernail, of the lower extremities. Petechial hemorrhages were also found beneath the visceral pleura and pericardium, and more extensive hemorrhages in

the left kidney. Both suprarenal glands were dark red throughout, with tense capsules, the right weighing 9.407 g., the left 5.587. Little normal tissue was recognizable in either. The tonsils were both very large and ragged, and in the left were many caseous pockets. Microscopically, there were acute suppurative and hemorrhagic nephritis and

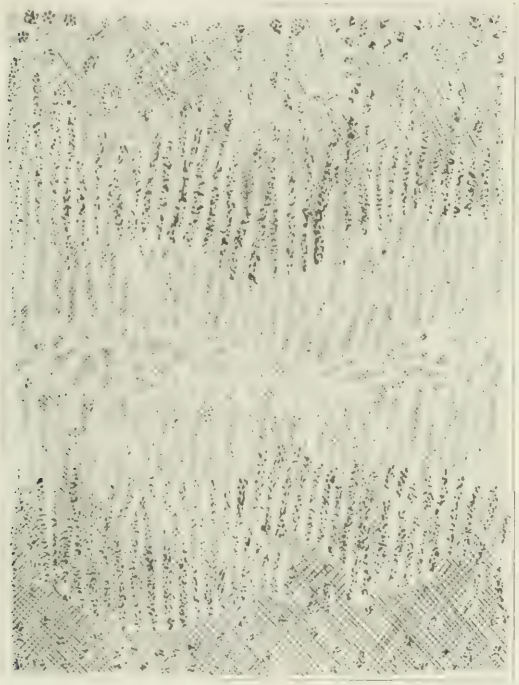


Fig. 2.—Diagram of a section of the suprarenal gland approximately 2 by 3 mm. The central part (pale gray) is full of blood from hemorrhage, and in this part of the adrenal very little medulla is present. The zones bordering this on each side with dark spots contain large amounts of fat (Sudan III stain), and the periphery of the cortex at top and bottom, represented here with crossed lines, contains the largest amount of hemorrhage.

adrenalitis. The hemorrhage was extensive in the glomerular and fasciculate zones of the cortices of the suprarenal glands, and there were multiple minute abscesses.

The first case, with coma, according to the classification given is of the nervous type, the second probably of the type with purpuric rash and hemorrhages in the abdominal organs. In both death followed the onset of acute symptoms quickly and there was cyanosis with marked embarrassment of the circulation and respiration. In both, the hemorrhage in the suprarenal glands was marked in the cortex and there was infection in the glands. The symptoms in each were much the same as those usually reported when the medulla has been most affected. In these two instances it seems not improbable that death may have been due to the sudden liberation of some cortical substance in the blood stream, or more probably, perhaps, in the light of recent demonstrations of the importance for life of the cortex in animals,[9] to a sudden interruption of the indispensable function of the suprarenal cortex.

December 10, 1923.

THE PRESENT STATUS OF FOOD POISONING IN THE UNITED STATES *

J. C. GEIGER

Epidemiologist, U. S. Public Health Service

In reviewing this subject Geiger said that reliable facts concerning the prevalence of food poisoning in the United States are difficult to obtain since the disease is rarely made reportable. Outbreaks of food poisoning are explosive in character, usually short of duration and frequently disregarded, unless there are spectacular features or the outbreak is botulism, in which event the attention attracted may be out of all proportion to the recorded morbidity and mortality.

Botulism is at present and perhaps has always been a comparatively rare disease in the United States. There

---

* Abstract of address given at a joint meeting of the Chicago Medical and Chicago Pathological Societies, Jan. 16, 1924.

9. Houssay, B. A., and Lewis, T. J.: The Relative Importance to Life of the Cortex and the Medulla of the Adrenal Glands, Am. J. Physiol. **64**: 512-521, 1923.

have been reported in the United States from 1899 to date, 129 outbreaks; a total of 435 people with 290 deaths, giving a case mortality of 67.1 and of which 45 outbreaks, or approximately one-third, have been proved toxicologically and bacteriologically. Thirty-one outbreaks were reported from western states in 1922 and 1923, two other outbreaks were from food canned in the west. In all the assembled data there had been only three outbreaks reported in southern states, in one of which the food was canned in the west. The outbreaks due to home canned foods and those due to commercially canned are in the ratio of approximately 10 to 1. The majority of outbreaks have been due to underheated or underprocessed foods. Methods of canning must insure sufficient heat penetration and make allowance for altitude and the hydrogen-ion concentration of the product. Sanitation by the thorough cleansing, proper storage and the use of fresh products is primarily essential as a protection against botulinus spoilage. There have been no outbreaks of botulism traced to commercially canned food since February, 1922, while there have been in the same period 26 outbreaks attributed to home canned foods.

Extensive examinations have been made of soils in which certain vegetables have been grown which, after canning, had caused outbreaks of botulism in humans. Cultures of these soils were toxic and the toxin thus formed was neutralized by the corresponding type of botulinus antitoxin. The investigators suggested that possibly the manuring of the soil might be the medium of the pollution of the soil with the spore of B. botulinus. However, other investigators stated that in over 2,000 samples of soil and other agricultural products in the United States and in other samples from Canada, Alaska, Belgium, Denmark, England, the Netherlands, Switzerland, Hawaiian Islands and China that were examined, it was demonstrated that the spores of B. botulinus are widely distributed in nature. Alaskan soils appear to be singularly free from the spores. The spore was found in greatest abundance in uncultivated mountain soils and to the least extent in soils that had been intensively cultivated. Geiger and Benson have

demonstrated an intensive distribution in certain localities, particularly in the State of Washington. It is of special interest that they were able to demonstrate experimentally that both type A and type B, B. botulinus, may exist in the same soil sample, type A predominating in cultures when vegetables such as corn and string beans were planted together with the soil in the culture medium.

It has been shown that guinea pigs succumb to botulism when fed a large number of toxin-free spores Geiger stated that there is a vast difference in results depending on whether tonxin-free spores are fed or inoculated into guinea pigs, even when such spores have been saturated with specific antitoxin and have been incubated. Such spores when fed may remain dormant in the animal body and be recovered from various organs, on autopsy, without the animals showing any previous symptoms of the disease. Epidemiologically there is every indication that a true botulism infection never occurs in the human being and the symptoms are due to performed toxins in the food when ingested. However, Geiger reported that certain experiments indicate the possibility of the absorption of the toxin from mucous surfaces other than the gastrointestinal tract and from fresh wounds.

The short incubation period in food poisoning which is probably due to the paratyphoid group, the early recovery of the persons ill, the low mortality rate, the absence of continued temperatures, or other evidence of infection especially when the food ingested contains living organisms of the paratyphoid group, are suggestive evidence that these outbreaks are also intoxications.

In the majority of cases of botulism the incubation period is from 24 to 48 hours, though the onset may occur earlier or be delayed. The earliest onset in the recent outbreaks investigated was 16 hours and the longest 48. Gastrointestinal symptoms are not as rare as is sometimes thought, but are delayed much longer than those observed in outbreaks due to the type of food poisoning caused by the paratyphoid group. The characteristic evidences of the disease recorded in botulisms were quoted in their usual order as follows:

Delayed onset, marked muscular weakness, gastrointestinal symptoms, disturbances of vision with diplopia and bleparoptosis, loss of ability to swallow and talk, constipation, rapid pulse and subnormal temperature, rarely any pain, death from respiratory failure and a high mortality rate.

In the outbreaks due to the paratyphoid group the characteristic symptoms are: Sudden onset, nausea, vomiting, abdominal pain, prostration, diarrhea, rise of temperature, and a mortality from 0 to 1 per cent. Therefore, the difference, clinically, between these two types of food poisoning is distinct and should be easily recognized.

In the treatment Edmunds and Long have recommended artificial respiration and the careful administration of physostigmin. Geiger, however, believes that immobilization and quiet are indicated by the best means available. To these measures must primarily be added the use of specific types of antitoxin. As there seems to be some fixation of the toxin in the body and probably no increase after the poisonous food has been ingested, early administration of the antitoxin is desirable. This is very difficult for as a rule the disease is not recognized within 48 hours after the food has been consumed and this is not unlikely the time limit of the efficiency of the antitoxin. Type A, B. botulinus is by far the most predominant type demonstrable as causing the outbreaks in the United States, type B being exceedingly rare as a cause of the disease in humans.

In the majority of outbreaks of botulism the preserved foods responsible have been noted to be visibly spoiled. This spoilage may be a relative matter as the containers can be normal in appearance and the disintegration of the contents be even so slight that no abnormal odor or taste is detected. When the type of food poisoning is recognized as botulism, always suspect preserved foods and meat products, such as sausages. In the type of food poisoning due to the paratyphoid group always suspect freshly cooked or warmed over food, especially if there has been some period of incubation.

In autopsies it has been stated that B. botulinus types B and A were found in the intestinal contents of two cases out of four studied, in the intestinal wall itself in one case and from the liver in one case. Recently Geiger isolated B. botulinus, type A, from the stomach wall of a case dying of botulism but not from the stomach contents. The essayist has made an investigation of several cases of illness recently occurring in Chicago. On autopsy of one person that died, the anatomical findings and subsequent microscopical examination revealed thrombosis in the brain and other tissues and a diagnosis of botulism was suggested. It was later proved that those cases were not botulism.

Occasionally in outbreaks of botulism there is the history that some persons after consuming the poisonous food did not become ill. A search of the records revealed that in twelve outbreaks there were 29 people who supposedly ate the toxic food and were not affected. Aside from the possible mistake of the records several explanations have been offered for this phenomena; namely, either there may be a greater concentration of toxin in various parts of the preserved food in the container than in others, or there may be some immunity to the intoxication, or perhaps only one can of several that were served were toxic.

In outbreaks of food poisoning due to the contamination of the food with the organisms of the paratyphoid group every effort should be made to demonstrate the presence of filterable toxic substances in the causative food. Bacteriologic examinations of the food and excreta of the persons ill should be made. It was pointed out that the stools should be examined as early as possible, as negative results will probably be obtained if such examinations are not made within forty-eight hours after the ingestion of the food.

It has been suggested that tests be made of the blood sera of persons ill in outbreaks of food poisoning due to the paratyphoid group for the presence of agglutinins. The results so far obtained have been inconclusive and of doubtful value, because of the many contributory and dependent factors in this test, such as previous vaccination with triple typhoid vaccine, the

negative bacteriologic findings of a specific organism in the suspected food, the comparatively short duration of illness, the coagglutinins demonstrable among the members of the paratyphoid group and the absence of definite information as to such reaction in the normal individual.

DISCUSSION

Dr. John L. White said that considerable publicity had been given the question of food poisoning by the press of the country and the laity attribute all gastro-intestinal irritations accompanied by headache, nausea and vomiting to the consumption of food. The press has popularized the diagnosis by calling these cases "ptomaine poisoning" and the public usually attribute this ptomaine poisoning to canned goods, with the result that there has been considerable detriment to the canning industry. When the ruling was made concerning the canning of olives, the firm most affected by the ruling insisted that the so-called basal food products be investigated, and since that time considerable work has been done.

Dr. White thought it was interesting that many of these so-called food poisoning outbreaks are not substantiated by facts and that they are erroneously diagnosed. Since 1922, there has been no outbreak of food poisoning due to goods canned by any of the commercial concerns, the only outbreaks being due to home canned products.

The speaker emphasized the paratyphoid intoxications as well as the botulinus, and stated that most of the work had been done on botulism. One way to attack the problem is for physicians to report all food poisoning cases to the Health Department. There is a city ordinance which requires the reporting of all such cases and the Department is willing to cooperate in all of them. They have a bureau with trained men who will take the food to the laboratory where it can be thoroughly examined, which will aid greatly in putting the mattter on a scientific basis. In an investigation of 800 so-called food poisoning cases, 80 per cent. proved to be something else. He emphasized the fact that the Food Bureau of the Health Department is willing to cooperate with any physician if he will notify the Bureau early in these suspected cases. There is much work to be done; they must first establish a history of exposure to the food in question, isolate the organism, identify the organism by agglutinin blood examinations and so on, and if they are able to do this they can definitely state that the food in question was the cause of the illness. By such measures the whole question of food poisoning can be placed on a scientific rather than a newspaper basis.

Dr. Edward M. Mikkelsen asked if there was anything in the way of drugs which might be of value in these cases, assuming that the antitoxin could not be procured early enough to be of value.

Dr. Geiger, in closing, said that he had never been able to find anything in the way of drugs which had been of value. Physostigmin has been suggested but he did not know of any basis for its use. Atropin had been used in several cases and in one or two instances was said to have done some good. Many things had been tried, but they were just "shooting in the dark" and trying to neutralize the poisoning as best they could. One thing indicated is elimination, but if the toxin has become fixed in the body he knew of nothing that could be of assistance. There is much to be learned about the treatment of botulism, but the outcome in these cases is so unfortunate and so rapid that there is usually no time to make an investigation before death ensues.

PYAEMIA DUE TO STAPHYLOCOCCUS ALBUS FOLLOWING ABORTION

OWEN HOMME AND THURE A. NORDLANDER

From the Pathological Laboratory, Rush Medical College

H. M., female, aged 19, entered the Cook County Hospital to the service of Dr. Goldsmith. Death occurred at the end of nine days, with no symptoms calling for specific attention except an intermittent mental involvement, manifesting itself in periods of irrationality, and the complaints of pain in the chest, chills and fever, with some cough.

Necropsy (Dr. E. R. LeCount) yielded the following anatomic diagnosis: Retention of placental tissue; gangrenous and suppurative endometritis; suppurative vulvo-vaginitis; bilateral stayphylococcic salpingitis and oophoritis; acute pyelo-uretero-cystitis; bilateral ovarian suppurative thrombophlebitis; occluding thrombus at the mouth of the right ovarian vein; thrombosis of the left renal vein; multiple metastatic abscesses of the kidneys; septic thrombosis of the ovarian veins; multiple metastatic abscesses of both lungs, liver and thyroid gland; thrombosis of the terminal radices of the pulmonary arteries; suppurative pelvic peritonitis; suppurative thrombophlebitis (staphylococcic); hemorrhagic infarcts of the liver; acute catarrhal tracheitis and bronchitis; acute hyperplasia of the tracheo-bronchial and biliary lymph

glands; passive hyperemia and edema of the lungs, edema of the leptomeninges; slight chronic passive hyperemia of the liver; cloudy swelling of the liver and kidneys; fatty changes of the liver; fibrous adhesions between the appendix vermiformis and right broad ligament; petechial hemorrhages of the stomach and duodenum; marked hyperplasia of the spleen; fibrous adhesions between the rectum, fallopian tubes and uterus; fibromyomata of the uterus; healed laceration of the cervix; generalized anemia; fibrinous pleuritis; sclerosis of the anterior mitral leaflet and the first part of the aorta; bruise abrasion of the right hip; pressure abrasions of the buttocks; veno-puncture needle wound of the right cubital fossa; secreting mammary glands; pregnancy pigmentation of the nipples; pregnancy hyperplasia of the thyroid gland.

Bacteriological Examination.—Cultures taken from the lung abscesses revealed at the end of twenty-four hours incubation at 37.5 C. on blood-agar media, typical staphylococcus albus colonies in pure culture. Microscopic examination of the twelve films taken from as many abscesses showed large, round Gram positive cocci grouped in typical cluster. Hanging drop examination revealed no motility. Transfers were made to other media. Litmus milk was slowly acidified and coagulated at the end of seventy-two hours. On potato media, the growth was profuse and non-pigmented. Inoculation into beef broth containing 20 per cent. sodium taurocholate did not lead to the disintegration of the organism at the end of forty-eight hours. Stab cultures in dextrose agar tubes resulted in a slight gas formation at the end of forty-eight hours. Gelatine was slightly liquefied at the end of ninety-six hours. Inoculation of guinea-pigs gave the following data:

Pig 1.—Intraperitoneal injection of a suspension of a twenty-four hour plain agar growth in normal salt solution caused death in twenty-four hours. Postmortem examination revealed a fibrino-purulent peritonitis. Cultures grown from the peritoneal fluid and heart's blood showed characteristic staphylococcus albus growths. Stained films revealed Gram positive cocci. They were found to be somewhat smaller than those in the films made directly from the lung abscesses.

Pig 2.—A subcutaneous injection of a suspension of a twenty-four hour plain agar growth in normal salt solution produced an abscess at the site of injection, one centimeter in diameter. The pig was killed at the end of five days. Pure cultures of staphylococcus albus were obtained from the subcutaneous abscess. Films showed the presence of staphylococcus.

Pig 4.—An inoculation was made intraperitoneally with two loops full of an attentuated growth on plain agar suspended in normal salt solution. This pig died at the end of three

weeks. No abscesses were found macroscopically. Blood cultures revealed the same organism, except that they seemed smaller than the original cocci, but in staining and cultural characteristics they were identical.

The literature reveals only eight fatal cases of staphylococcus albus bacteremia. Two cases were reported by Lexer; two by Landau; one by Southard and Fitzgerald; one by Bassoe; one by Holmes; one by Coutois-Suffit and Beaufume. This last one was complicated by the symbiosis with gonococci. Other cases are reported without classification of the type of staphylococcus, and are not considered in this paper.

From the eight fatal cases reported in the literature it would be impossible to draw any conclusions concerning the age and sex incidence. Ages and sex ranged as follows: (1) female, 10 years; (2) female, 12 years; (3) male, 19 years; (4) male, 38 years; (5) female, 39 years; (6) female, 42 years; (7 and 8) cases by Lexer without age or sex specified.

The cause of staphylococcus albus bacteremia is variable. Phemister holds that the skin may be the original focus in staphylococcus albus osteomyelitis. He arrives at this conclusion from the study of three such cases which gave definite histories of an initial skin injury and infection. He feels that such skin foci are often neglected in favor of the generally conceded nasopharyngeal foci. This view is substantiated by the cases of Landau, in which furuncles were established as the original foci. Holmes believes that the bacteria were introduced in his case by infected diphtheria antitoxin. Contributing causes are here as elsewhere lowered resistance of the individual and increased virulence of the organism.

It is obvious that the symptoms are variable dependent upon the severity of the bacteremia. Reviewing the symptoms of the cases in the literature we find that the only symptoms common to all cases are those referable to a terminal mental involvement variously described as "acute delirium," "typhoidal sex state," "delirious euphoria," "coma" and "insanity and amnesia."

The early manifestations are "biliousness," "Malaise," "neurasthenia," "headaches," "nervousness,"

"insomnia," "constipation," eroticism." In all cases there was an intermittent fever, varying from 100 degrees to 104 degrees as a maximum, with proportionate increase in the heart rate and respiration. In the five cases which came to postmortem examination, the only anatomic changes common to all of them were multiple abscesses and fibrino-purulent pleurites.

Bacteriological examination in all the above cases revealed staphylococcus albus in pure culture. Cleland was able to culture both ante- and postmortemly the organism from the pleural fluid. Landau obtained pure staphylococcus albus from the facial abscesses and the blood ante mortem. Coutois-Suffit and Beaufume obtained pure cultures in life from the blood and from the abscess of the triceps and pleural effusions. Post mortem they again obtained pure cultures, from the blood, heart and from the retrosternal and retrorenal abscesses. E. E. Southard and Fitzgerald obtained pure cultures from the hearts blood and from the brain. Their cultures produced no effect when injected intraperitoneally and subcutaneously into guinea pigs but did lead to an extension meningitis when injected into the infraocular tissues of the orbit. Bassoe obtained pure cultures from the bile, blood, pleural effusion, pus from the lip abscess, and from emulsions of the liver, spleen and lungs. Intravenous injection into rabbits resulted in deaths in one month from ascending paralysis. Lexer cultured the organism in pure state from the blood in two cases.

These findings are contrary to the opinion of Libman, who, following an extensive study of staphylococcus bacteremias, was led to believe staphylococcus albus bacteremias were of agonal origin only. It is interesting to note that in the cases of Landau, both patients while having positive blood cultures intermittently gave no clinical symptoms. He feels that this phenomena is due to a loss of virulence of the organism. The fact that forty-eight hours were required before the cultures showed any growth he claims as further substantiation of the lowered virulence of the organism. He feels also that metastatic abscesses may, but do not necessarily result from staphylococcus albus bacteremias. The bacteremia may be the result of the abscess or vice

versa. Southard and Fitzgerald feel that these bacteremias may be the causative factors in certain cases of "acute delirium" of unknown origin, and that study of blood cultures of all insane might reveal a type of bacteremic insanity.

This type of pyaemia, according to the recent investigations of Moody, is rare. This investigator finds that the common organism is the streptococcus.

Bassoe, P.: Staphylococcus Albus Carbuncle Resulting in Death. Trans. Chicago Path. Soc. **4**: 331-336, 1903-6.

Bjorkenheim, E. A.: Bacteriologie und Therapie des Fieberhaften Abortes. Arch. f. Gynak., Berlin **98**, 1912.

Cleland, J. Burton.: Sudden Death Due to Staphylococcus Pneumonia and Pleurisy, Australasian M. Gaz., Sydney **28**: 303, 1909.

Holmes, C. R.: A Fatal Case of Cryptogenic Staphylococcus Bacteremia, Lancet Clinic, Cincinnati **59**: 229-230, 1907.

Landau, Hans: Non Hemolysing Staphylococcus Albus Septicemia, Deutsch. med. Wchnschr., Leipsig, 1921-1061.

Lexer, E.: Two Cases of Staphylococcus Albus Bacteremia. System of Practical Surgery, Bergmann, Bruns and Mickulicz, American edition, Volume 479.

Libman, E.: Staphylococcus (Aureus) Bacteremia. Med. News, New York, April 18, 1903, p. 773.

Phemister, D. B.: Hematogenous Staphylococcus Infection Secondary to Foci in the Skin, J. A. M. A. **78**: 480-483.

Palier, E.: Die Umwandlung der Staphylococcus aureus in Staphylococcus Albus, München. med. Wchnschr., Munich, 1911.

Potocki, P.: Bacteriologie sanguine dans l'infection puerperal Annales de gynecologie et d'obstetrice, Paris **43**: 129-140, 1918.

Southard, E. E., and Fitzgerald, J. G.: Discussion of the Psychic and Somatic Factors in a Case of Acute Delirium Dying of Septicaemia. Note on Experimental Guinea-Pig Infection with Staphylococcus Albus, Boston M. & S. J. **112**: 452-458, 1910.

Courtois-Suffit and Beaufume, S.: Infection generalissee mortelle a gonocoque et a staphylococcgue. Bull. et mém. Soc. méd. d. hôp. de Paris **22**: 352-358, 1905, E. 3S.

February 11, 1924.

THE FORMATION OF ACCESSORY FOOD SUBSTANCES FOR YEAST BY B. COLI COMMUNIS

ROBERT C. ROBERTSON

A review of the origin of vitamins indicates that certain bacteria are a possible source of these substances.

In an endeavor to determine a possible role of B. Coli communis in forming these substances the following experiments were performed:

A synthetic medium was prepared of the following C. P. substances: asparagin 3.4 gms., calcium chloride

.1 gm., dextrose 20 gms., magnesium sulphate .2 gm., potassium phosphate (K_2HPO_4) 1 gm., sodium chloride 5 gms., sterile distilled water to 1 liter, autoclaved, titrated to Hp 7.6 and tubed.

When used as a medium on which baker's yeast was inoculated growth was not obtained beyond a few generations unless an aqueous vegetable extract was added in minute quantities, which resulted in luxuriant growth over an indefinite period of time; while B. coli communis when inoculated thereon grew luxuriantly for an indefinite time when transplanted every 48 hours without the addition of the aqueous extracts.

When the medium on which the 68th generation of B. coli had grown for 10 days, was filtered through a Berkefield filter and the filtrate then used as a medium on which washed yeast cells were inoculated with 48-hour transplants, a luxuriant growth was obtained over an indefinite period of time.

It would appear that baker's yeast is unable to synthesize its own accessory growth substances on this medium but that these substances are formed by the growth of B. coli thereon, the effect on the yeast growth then obtained closely resembling the result obtained by the addition of aqueous vegetable extracts.

February 11, 1924.

TRANSACTIONS OF THE
CHICAGO PATHOLOGICAL SOCIETY

Vol. XII June, 1, 1924 No. 11

PRIMARY CARCINOMA OF THE TRACHEA

WITH A REPORT OF A CASE

JESSIE ROBERTS BROMAN

Carcinoma is rarely found as a primary lesion of the trachea. About fifty-eight fairly authentic cases were found in the literature of the past fifty years. These were reviewed and tabulated on the basis of such data as the size, location, age, sex, duration of symptoms, histology, and final outcome of the case, with such necropsy reports as were available.

The most usual location was found to be on the posterior wall just above the bifurcation of the trachea. Being without striking symptoms, many of the cases were not diagnosed correctly until postmortem examination. The histology was very variable.

The case reported was one of a series of routine necropsies done by Dr. H. G. Wells at the Cook County Hospital. It was the only tracheal carcinoma, primarily involving that site, in 545 malignancies. In this and other series, the ratio between primary carcinoma of the trachea and primary carcinoma of the larynx, was as 1 to 4. The growth was on the posterior wall at the bifurcation. Histologically, it was made up of round and spindle cells, considerable fibroplastic reaction and marked necrosis down to the cartilages of the trachea. Typical metastatic growths were found in many of the organs.

A complete report, with review of the literature, will appear in the *Journal of Cancer Research* at a later date.

Oct. 8, 1923.

VARIATIONS IN THE ANASTOMOSES OF THE CORONARY ARTERIES AND THEIR SEQUENCES

H. A. OBERHELMAN
AND
E. R. LECOUNT
From the pathologic laboratories of Rush Medical College, and the Presbyterian Hospital, Chicago

Anastomoses between the branches of the coronary arteries and with the arteries of surrounding structures have been quite definitely established by experimental ligation in animals, clinical observations combined with necropsy dissection, injection of the coronary arteries with subsequent corrosion of the extravascular tissues of both normal and diseased human hearts, and roentgenologic studies. Such studies have been made over a long period. Many of the earliest investigators failed to draw any conclusions at all regarding anastomoses, and simply noted that the animals died. Among these are Chirac,[1] who used dogs, and Ericksen [2] and Panum,[3] who used both dogs and rabbits. Panum's experiments made with living animals were ingenious, for he put black melted wax into the innominate vein and then clamped the aorta to secure its entrance into the coronary arteries. In 1880, Samuelson and Bezold,[4] also using dogs and rabbits, concluded that the coronary arteries must vary to account for death following ligation.

A terminal nature of the circulation dependent on "end arteries" was probably first applied to the coronary arteries by Cohnheim,[5] because by ligating one or another coronary artery in curarized dogs he brought the heart to a standstill in two minutes. His conclu-

1. Cited by Gross, Louis: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B. Hoeber, 1921.
2. Ericksen: On the Influence of the Coronary Circulation on the Action of the Heart, London M. Gaz. **2**: 561, 1842.
3. Panum: Experimentelle Beitrage zur Lehre von der Embolie, Virchows Arch. f. path. Anat. **26**: 311, 1862.
4. Samuelson and Bezold, cited by Cohnheim (Footnote 5).
5. Cohnheim: Ueber die Folgen der Kranzarterien Verschliessung für das Herz, Virchows Arch. f. Path. Anat. **85**: 502, 1881.

sions were modified by Kolster [6] and later by Porter,[7] who, by studying infarct formation by coronary ligation in dogs, found that the animals did not necessarily die. The reason for this was demonstrated by Spalteholz [8] and by Hirsch,[9] who found after coronary ligation in dogs and monkeys that the region infarcted was always smaller than the region supplied by the ligated artery. Just what branches of the coronary arteries that could be soligated and cause no myocardial standstill was subsequently studied by Miller and Matthews,[10] who, in addition to confirming the work of Spalteholz, found no serious disturbance of the heart in dogs following the ligation of the left coronary artery, provided the ligation was distal to the septal branch.

By dissection of human hearts, Thebesius [11] and later Haller [12] and Morgagni [1] called attention to anastomoses between the coronary arteries. Early in the nineteenth century, Caldini [1] found similar anastomoses, and in the latter part of that century, Beraud and Langer [1] first demonstrated anastomoses between the coronary arteries and those of adjacent structures.

The inadequacy of communicating branches in human hearts is well demonstrated by the scars of the myocardium following partial or total occlusion of one or another coronary artery. This Huber [13] recognized from the study of seventeen human hearts removed from the bodies of persons dying of coronary arterial disease, either suddenly or several hours or days after the acute attack, and in all he found myocardial scars. Silverthorn [14] arrived at a similar conclusion from the study of one human heart with total thrombus occlusion

6. Kolster: Experimentelle Beitrage zur Lehre der Myomalacia Cordis, Skandin. Arch. f. Physiol. **4**: 1, 1892.
7. Results of Ligation of the Coronary Arteries, J. Exper. Med. **1**: 46, 1896.
8. Spalteholz: Die Coronararterien des Herzens, Anat. Anz. **30**: 141, 1906.
9. Hirsch: Coronararterien in Herzmuskel, Deutsch. med. Wchnschr. **20**: 790, 1907.
10. Miller, J. L., and Matthews, S. A.: Effect on the Heart of Experimental Obstruction of the Left Coronary Artery, Arch. Int. Med. **3**: 476 (June) 1909.
11. Cited by Spalteholz (Footnote 8).
12. Haller, cited by Amenomiya: Virchows Arch. f. path. Anat. **199**: 87, 1919.
13. Huber: Einfluss der Kranzarterienerkrankungen auf das Herz, Virchows Arch. f. path. Anat. **89**: 236, 1882.
14. Silverthorn: Disease of the Coronary Arteries and Its Effects, Canadian Practitioner **23**: 193, 1898.

of the mouth of the left coronary artery. Barth,[15] from the study of a thrombus-occluded right coronary artery, even went so far as to favor Cohnheim's [5] view of "end arteries." One of us,[16] in discussing the pathology of angina pectoris, studied sixty human hearts removed from the bodies of persons who died from difficulty with the circulation of blood in the coronary arteries, or with lesions generally regarded as caused by such difficulty. Thirty-four were due to fibrous myocarditis with sclerosis of the coronary arteries, and twenty-six to more or less acute occlusion by thrombosis or embolism. The conclusion was that, although collateral anastomoses existed between the coronary arteries and those of adjacent structures, yet with sclerosis or with more acutely developing obstruction from other causes, the compensatory circulation may prove inadequate or not be established promptly enough to prevent sudden death.

That gradualness of occlusion of a coronary artery is important for the development of an adequate collateral anastomosis was first recognized by Galli,[17] who found no gross or microscopic change of the myocardium following total occlusion of the mouth of the right coronary artery. Merkel [18] likewise found no myocardial change following gradual occlusion of the left. It would seem, then, that an absence of myocardial change following occlusion of a coronary artery demands that the occlusion be brought about slowly.

This opinion received support from the study by Amenomiya [19] of the relationship between the papillary muscles and diseased coronary arteries in eleven human hearts removed from the bodies of patients who died from heart failure. He found either infarcts or wedge-shaped scars, which he ascribed to a sudden occlusion of

15. Barth: Plötzlicher Tod durch Verstöpfung der Kranzarterie, Deutsch. med. Wchnschr. **22**: 269, 1896.
16. LeCount, E. R.: Pathology of Angina Pectoris, J. A. M. A. **70**: 974 (April 6) 1918.
17. Galli: Ueber anastomotische Zirkulation des Herzens, München. med. Wchnschr. **50**: 46, 1903.
18. Merkel: Zur Kentniss der Kranzarterien der menschlichen Herzens, Verhandl. d. path. Gesellsch. Stuttgart **10**: 127, 1906.
19. Amenomiya: Ueber die Beziehungen zwischen Koronararterien in papillar Muskeln in Herzen, Virchows Arch. f. path. Anat. **199**: 87, 1919.

a relatively large artery. Herrick,[20] from clinical observations, arrived at the conclusion that the variation in anastomoses, the size of the vessel occluded and the condition of the remaining branches are all factors related to a failure for death to result abruptly with coronary artery thrombosis or embolism.

The new corrosion methods, first, though crudely, introduced by Hyrtl,[11] marked the beginning of a more thorough understanding of coronary anastomoses. He injected a metallic alloy with a low melting point, and then digested the extravascular tissues with acids. Merkel [18] first used substances for injection impenetrable to the roentgen ray, and in thirty-four normal and diseased human hearts was able to demonstrate anastomoses. He also observed that the left coronary artery filled when injection was made through the mouth of the right.

The following year, Merkel's [18] work was confirmed by Spalteholz,[8] who, in addition to having made experimental ligations of coronary arteries in dogs, used chrome yellow and gelatin for injection purposes and then digested the extravascular tissues by acids. He studied twenty-eight human hearts, and located the anastomoses beneath the epicardium and endocardium and in the muscle substance. Using the same method and eighteen human hearts, von Redwitz [21] confirmed the observations of Spalteholz, and concluded that the coronary arteries are not end arteries, but, when suddenly occluded, may cause ischemic changes, which are not likely with slow occlusion.

Nussbaum [22] found that it was impossible to inject completely all the capillaries of the coronary arteries with liquid petrolatum. He concluded that the nastomoses are not functionally adequate, and that to prevent death from myocardial infarction the anastomosing vessel must have the same diameter as the one occluded.

20. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**: 2015 (Dec. 7) 1912.
21. Von Redwitz: Der Einfluss der Erkrankungen der Coronararterien auf die Herzmuskeln mit besonderer Berücksichtigung der chronischen Aortitis, Virchows Arch. f. path. Anat. **197**: 432, 1909.
22. Nussbaum: Ueber das Gefasssystem des Herzens, Arch. f. mikr. Anat. **80**: 450, 1912.

On the other hand, Smith,[23] using barium sulphate, supplemented with stereoscopic roentgenograms, found in normal human and dog hearts anastomoses mainly between many small vessels, which he believed numerous and large enough to function.

Recently Crainicanu [24] and also Gross [25] have studied the arrangement of the blood vessels of the heart, using roentgenograms after such injections and corrosion methods as have been mentioned. Crainicanu found anastomoses in the septum, walls of the ventricles, region of the Kieth-Flack node and the papillary muscles. Gross came to the conclusion that the heart is abundantly provided with capillary and precapillary anastomoses which are normally not in use, so that they are inadequate for emergencies but may become adequate with gradual obstruction.

It is apparent from the conclusions arrived at by the various investigators mentioned and by the use of a number of different methods that the idea of an absence of alteration of the myocardium with the gradual occlusion of the main branch of one coronary artery has finally won considerable approval. Its acceptance has come largely from the reports of careful studies of single cases, such as those of Galli,[17] who found an occlusion due to sclerosis and fresh thrombus formation; of Merkel [18] with total occlusion from sclerosis; of Grayston [26] with occlusion due to an aneurysm, and that reported by one of us [27] of occlusion of the right coronary artery mouth by syphilis.

Some of the difficulty in understanding coronary disease of the human heart and its sequences is directly attributable to a general disposition to regard the coronary arteries and their entire arterial bed as an anatomic "invariable," whereas such is certainly not the case. Not only are there variations which we must admit are consistent with normal conditions, but a still greater

23. Smith, F. M.: Concerning the Anatomy of the Coronary Arteries, Am. J. M. Sc. **156**: 706 (Nov.) 1918.
24. Crainicanu, A.: Anatomische Studien über die Coronararterien und experimentelle Untersuchungen über ihre Durchgängigkeit, Virchows Arch. f. path. Anat. **238**: 1, 1922.
25. Gross, Louis: The Blood Supply to the Heart in Its Anatomic and Clinical Aspects, New York, Paul B. Hoeber, 1921.
26. Grayston: Cook County Hospital Rep. **3**: 280, 1906.
27. Oberhelman, H. A.: Tr. Chicago Path. Soc. **53**: 57, 1919.

variation is brought about by disease; and these two sorts of variations altogether include a great many differences in the size, number and distribution of the

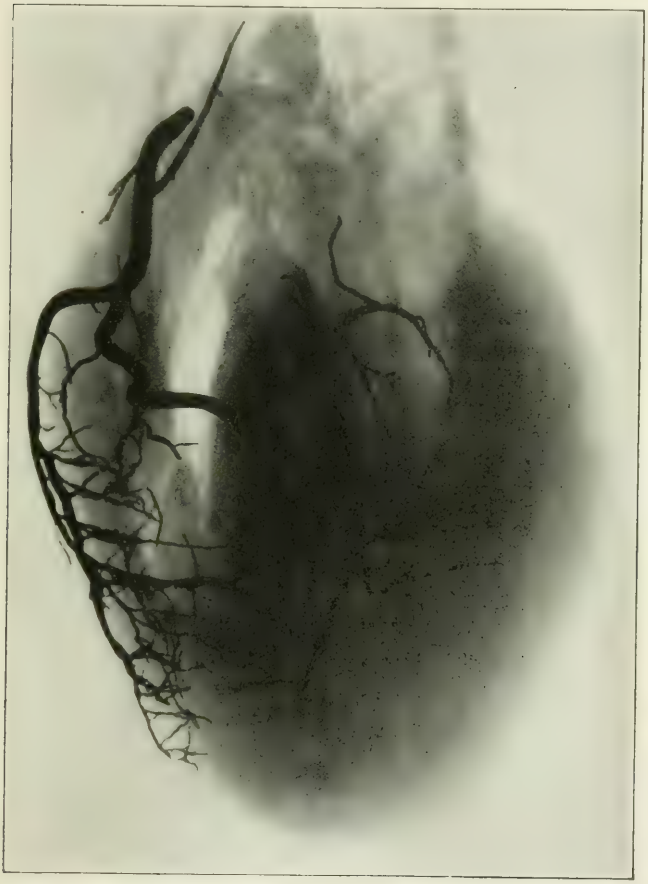


Fig. 1.—Right coronary artery of normal human heart injected with mercury.

branches of the coronary arteries, which may either play a rôle in collateral circulation when the blood supply through one coronary is abruptly interfered

with, or by their total or partial absence prevent any such compensation, and these are well brought out by the following examination.

Fig. 2.—Right and left coronary arteries injected.

Twenty-six human hearts were studied, mostly from males between the ages of 15 and 70 years. They were removed by cutting widely through the large vessels

and then placed in the icebox for from twelve to twenty-four hours to allow rigor mortis to disappear. All were injected with metallic mercury, under a pressure of from 125 to 150 mm., through a cannula tied into the

Fig. 3.—Normal human heart without demonstrable precapillary anastomosis.

mouth of one coronary artery. A number of injections were made under the fluoroscope. In some the mercury broke through the subendocardial vessels and escaped into the ventricles. In seventeen, the entire arterial system filled through the mouth of one artery,

the mercury appearing at the mouth of the other in from one to three minutes. In nine, both arteries had to be injected separately to fill the arterial system, even after prolonged injection through the mouth of one. Stereoscopic roentgenograms were made of each heart and from different angles. In a few of the nine hearts, after the filling of one artery (Fig. 1), plates were made before injecting the other (Fig. 2). After such examinations, pieces were taken from the base, middle and apex of the left ventricle, the septum and right ventricle for microscopic examination.

In one group of nine hearts there was no evidence of collateral anastomoses (Fig. 3), myocardial disease or arterial change except for a few small, widely scattered, soft, yellow places in the large arteries of one heart. Both arteries of these nine hearts had to be injected separately to fill the arterial system. The absence of demonstrable anastomoses, according to some investigators, may be due to the inability of the heavy metal to penetrate the finer capillary network, the precapillary network alone being demonstrated. The only deduction warranted is that, with the method employed, there were neither capillary nor precapillary anastomoses demonstrable in these hearts. They were obtained from the bodies of persons between the ages of 15 and 55, most of whom died from external violence, and none from causes affecting the heart or its blood supply. In these hearts there was no lesion for which a collateral anastomosis was needed, and the conditions were all consistent with health, with the trivial exception noted. The outstanding feature of these nine hearts is the absence of branches connecting the two arteries, and concerning this there are two noteworthy comments: that (1) with sudden obstruction of the circulation in one artery the other would most certainly have been inadequate, and (2) with gradual occlusion the development of an adequate collateral circulation might have resulted.

In another group of five hearts there was no myocardial or arterial disease, and in these respects they were essentially like the nine just mentioned, but in addition possessed definitely demonstrable anastomoses because

(1) the entire arterial system filled through the mouth of one artery; (2) the mercury was seen passing from the branches of one into those of the other with the aid of the fluoroscope, and (3) a greater anastomosing network was found (Fig. 4). These hearts were removed

Fig. 4.—Normal human heart whose arterial system filled through the mouth of one artery with moderate degree of anastomosing vessels.

from the bodies of persons between the ages of 30 and 50 years who died either from external violence, disease or other condition which failed to alter the heart or its circulation. In one death (from barbital poisoning) the right coronary was definitely small and the left comparatively large, and in another the reverse

obtained. In two the anastomoses occurred between the right coronary and left descending branch, in two others between the right coronary and left circumflex branch, and in one between the right coronary and both left

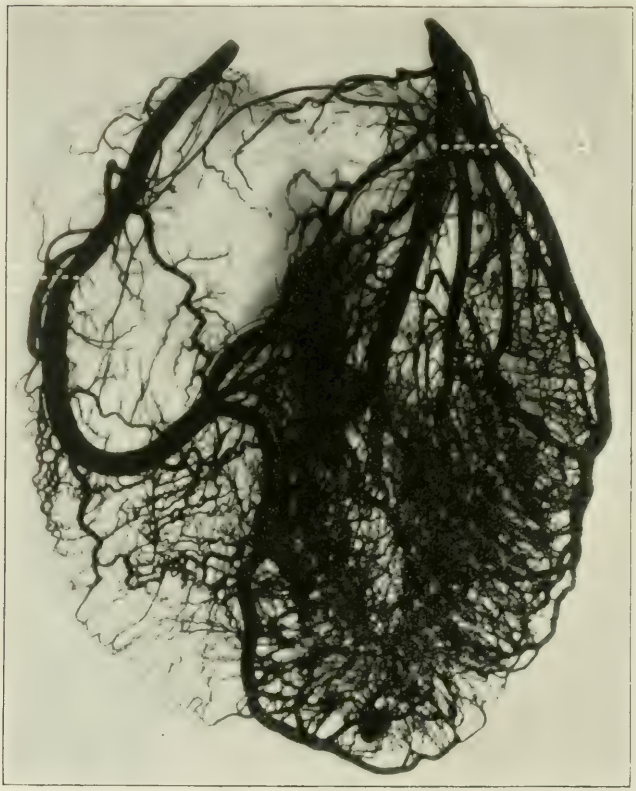


Fig. 5.—Human heart with narrowing (*A*) of the left descending and (*B*) of the right coronary artery by calcium, with extensive collateral anastomosis in the septum and wall of the left ventricle and apex.

descending and circumflex branches. In these five hearts there was likewise no lesion for which a collateral anastomosis was needed, but nevertheless a definite collateral circulation was demonstrable, and it

may be assumed that the arteries in these five hearts would have allowed a far more adequate anastomosis to maintain function and preservation of the myocardium with either sudden or gradual occlusion.

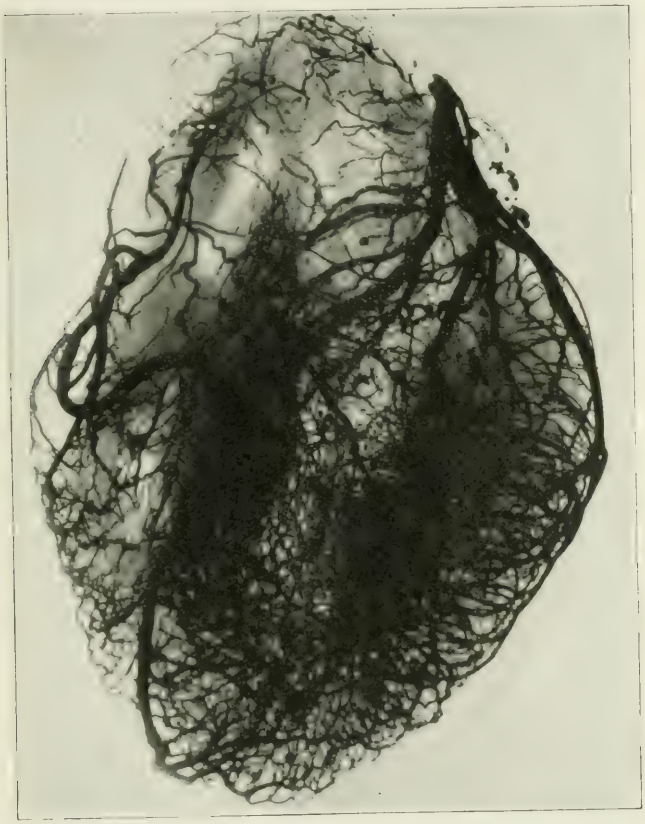


Fig. 6.—Human heart with total occlusion of the right coronary artery mouth (*A*) and a small right coronary artery; abundant anastomosis in the septum, apex and left ventricular wall.

In a third group of four hearts there was no myocardial change either grossly or microscopically, but diseased arteries were present with definitely demonstrable

collateral anastomosis (Fig. 5). They were removed from the bodies of persons between the ages of 20 and 65 years, two dying from interference of coronary circulation, one from influenzal pneumonia, and one from external violence. In two, the arteries were definitely calcified, with narrowing of the lumen with anastomoses demonstrable between the right coronary and left descending branch; in one, the mouth of the right coronary was narrowed to 1 mm. in diameter by syphilis, and with anastomoses between the right coronary and both left descending and circumflex branches; in another, the arteries were partially calcified, with narrowing and with anastomoses demonstrable in the same region. In these hearts there was a need for collateral circulation that was adequate entirely to preserve the myocardium and maintain function for some time. The occluding process in these hearts was slow, and therefore allowed the arteries to develop a maximum measure of safety. These conditions in these four may be regarded as examples of what might have taken place in the hearts of the second group, had a need for a greater collateral circulation arisen.

In a final group of eight hearts there were extensive myocardial changes, almost or total occlusion of one or another artery, and abundant collateral circulation. They came from the bodies of persons between the ages of 42 and 70 years, whose deaths were either sudden or a matter of only a few hours. In six, the coronary arteries were markedly calcified with definite narrowing, with the occlusion in two made complete by a fresh thrombus, and in these six the anastomoses had developed between the right coronary and both left descending and circumflex branches. Of the remaining two, the mouth of the right coronary was almost occluded in one and completely occluded in the other (Fig. 6) by syphilis, and in these the collateral anastomoses occurred between the right coronary and left descending branch. The myocardial changes of this group consisted generally of scar tissue, necrosis, hemorrhage and cellular infiltration, and the regions involved correspond to the regions supplied by the involved arteries, but are always much smaller. In these hearts there was

likewise a need for a collateral circulation which was adequate but only for a time, death being more or less sudden.

SUMMARY

1. A precapillary anastomosis between the branches of the two coronary arteries is shown by the escape of metallic mercury from the mouth of one of them in from one to three minutes after its introduction in the other with from 125 to 150 mm. of pressure, and when observed under the fluoroscope this demonstration is most convincing.

2. There are at least two factors concerned with disease of the coronary arteries and its sequences which are highly important, and each possesses so much of variation that they are strictly comparable to the "variables" of mathematics. One is the considerable difference that the arterial bed of the myocardium may possess normally as to anastomosis between the branches of the two coronary articles. The other is the time element, whether narrowing in the channels of the branches of either or both arteries, or total occlusion by any process whatsoever occurs abruptly or slowly; for, with the more gradual occlusion, a marked compensatory anastomosis may be developed.

We suggest that failure to recognize the inconstancy of these two factors is in part responsible for the large literature dealing with the subject, and for many of the misunderstandings with which it has been involved.

Nov. 12, 1923.

FUNDAMENTAL HARMONY SHOWN IN ALL ESSENTIALS IN SPONTANEOUS NEOPLASMS AND IN TRUE EXPERIMENTAL TUMORS

MAUD SLYE

From the Cancer Laboratory of the Otho S. A. Sprague Memorial Institute and the University of Chicago

The intensive study of any medical problem along many widely divergent lines is likely to bring out a mass of facts which may seem somewhat antagonistic, when

viewed superficially. Such a situation has arisen at the present time in the field of cancer research, and there is, therefore, a need for synthetic consideration of these apparently divergent facts, which are divergent in appearance only.

It is the aim of this paper to give such synthetic consideration to two of these apparently divergent facts brought out by cancer research and to suggest some of the missing links. I refer to the behavior of spontaneous new growths, and to that of experimentally produced tumors in some of their apparent differences, as shown in laboratory studies of both types of animal neoplasms.

I shall take as the main criterion of comparison, the inheritance behavior of the various types of tumor production, since the inheritance behavior of any organic character, or entity, is its biologic fundamental. As I pointed out in a preceding article,[1] the whole process of organic development represents the unbroken functioning of heredity in each minute and infinitely interrelated detail transmitting types of protoplasmic behavior from ancestor to offspring. So infinitely interrelated are the minutiae of organic life, that their behavior in heredity is very difficult of complete analysis. The ready conclusion, therefore, is frequently drawn that heredity does not underlie the behavior of all minutiae of organic life, because it is not always superficially apparent.

The logic of the matter is certainly evident: similar tissues must function in the same way unless they are forcibly prevented from doing so, because they were derived from a common ancestry with only a given type of possible behavior. That they can be forcibly prevented from doing so is no more to be disputed than that an infant's leg can be cut off and prevented from growing to the inherited length.

Let us consider in sequence the various types of artificially produced tumors and compare them with spontaneous neoplasms in some of their biologic fundamentals.

1. Biologic Evidence for the Inheritability of Cancer in Man, J. Can Res. **7**: 107, 1922.

I. TUMOR CELLS GROWING IN VITRO

When living tumor cells are placed in a test tube or other mechanical container and are given the right conditions of attachment and food [2] they perform the common inherited function of all nourished living cells. That is, they divide and the mass grows. We have here the neoplasm reduced to its lowest terms, and manifesting the only inherited behavior types possible in its restricted location, namely, the absorption of food and the undifferentiated mass growth by cell division, sarcoma cells producing undifferentiated sarcoma only, and carcinoma producing undifferentiated carcinoma.

There is nothing for the tumor to infiltrate into, and no organ for it to invade by metastasis. It merely grows according to its type, up to the limits set by its environment. Its cell division and mass growth are potentialities inherited from the original spontaneous tumor of which it was a part, and mean nothing with reference to the inheritance possibilities of its artificial host. If the food is withdrawn the tumor cells cease dividing and die. It thus manifests another type of inherited behavior of protoplasm. Its cessation of cell division and its death mean nothing with reference to inherited possibilities of the test tube. They are concerned only with the tumor cells.

II. GRAFTED TUMORS

When living tumor cells are grafted into a living host, and are given the right conditions of attachment and food, they also perform the common inherited function of all nourished living cells, that is, they divide and the mass grows. We have here a more complex problem of inheritance behavior than that furnished by the tumor cells growing in vitro. The behavior problem is now twofold: the inheritance behavior of the piece of tumor and the inheritance behavior of the living container into which it has been grafted.

The tumor tissue grafted into the living host manifests exactly the same fundamental types of inherited behavior shown by the tumor cells growing in vitro, namely, absorption of food with consequent cell division

2. Lambert, Hanes: J. Exper. M. **14**: 129, 1911.

and mass growth; and cessation of cell division with consequent death, when nutriment is withdrawn. Its cell division and mass growth and its death if nutriment is withdrawn mean nothing with reference to the inheritance possibilities of the living host into which the tumor has been grafted. Its inheritance potentialities are those of the tissues of the animal of which it was a spontaneous tumor, not those of the tissues of its host. Here, also, as in the case of the tumor cells growing in the test tube, the cell mass, when given proper conditions of attachment and food, grows without differentiation and without control up to the limits set by its environment.

The environment of the grafted tumor, however, instead of being a mechanical container, is a living organism with inheritance potentialities of its own, which must determine the limits set for the growth of the parasitic tumor, but not the fact or the type of the growth itself. If the host normally regenerates its own cells, assaulted by the inoculation, and builds up an accessory circulatory system for the graft so that nutriment is supplied, the cells of the parasitic tumor continue their division and mass growth. If the adjacent tissues of the host do not regenerate and do not build up an accessory circulatory system, no nutriment is furnished the parasitic cells, that is, they are not given proper conditions of attachment and food, and consequent cell death occurs with the sloughing out of the graft. That is, we do not get "a take." "A take" of grafted tumor, fundamentally, then, depends on the *normal regeneration* of the assaulted tissues, and not on the abnormal growth of the host cells.

Following the demonstrations by Loeb and by Jensen, about 1900, showing the possibility of inoculating rat and mouse tumors, a great deal of work was done with such tumors, much of which concerned itself with the problem of the inheritability of cancer, notably the work of Tyzzer [3,4] and later of Little and Tyzzer.[5]

Since the beginning in this laboratory, of studies in the inheritability of spontaneous neoplasms, in 1910, the

3. J. M. Res. **16**: 519, 1909.
4. J. Cancer Res. **1**: 125, 1916.
5. J. Cancer Res. **6**: 106, 1921.

fundamental differences between spontaneous and grafted tumors have been made increasingly apparent.[6] No further evidence of the intrinsic difference between spontaneous and grafted tumors is needed than Tyzzer's own results in later obtaining spontaneous tumors in individuals which had refused grafts.[7] Bashford also reported that animals immune to inoculation, were capable of developing spontaneous tumors,[8] and others have made similar observations.

There undoubtedly is an interesting inheritance problem in these genetic studies carried on with transplanted tumors. It concerns itself, however, with the inheritability of tendencies of the assaulted tissues to regenerate normally and to build up an accessory circulatory system, and not with the inheritability of the tendency to regenerate abnormally, as is the case in cancer. A very large field of metabolic behavior is opened by these genetic studies of grafted tumors, but the inheritability of spontaneous cancer, and many other problems of spontaneous cancer behavior, do not lie within the field of grafted tumor studies.

Let us apply here the criterion of inheritance behavior between these grafted tumors and spontaneous animal tumors. Little and Tyzzer, who carried out the most extensive and conclusive of these genetic studies of grafted tumors, found that heredity controls the susceptibility to these tumors in various strains of mice, but that susceptibility and nonsusceptibility do not behave as unit characters, but rather as a complex of unit characters, probably many in number. Susceptibility to these grafted tumors uniformly appeared in the first hybrid generation in 100 per cent. of the cases, and in steadily decreasing frequency in later generations.

The appearance of susceptibility to grafted tumors in the first hybrid generation between pure stocks, would show that one of the most important factors concerned in the transmission of susceptibility to grafted tumors must be a dominant. The logic of the situation confirms this conclusion, for obviously the first and most impor-

6. J. Cancer Res. **5**: 72, 1920.
7. J. M. Res. **16**: 479, 1909.
8. Fourth Sc. Rep. Imp. Can. Res. Fund **19**: 1911.

tant factor in determining the acceptance of a graft, whether of tumor, of bone, or skin, or any other organic tissue, is the ability of the assaulted tissues to regenerate normally, and thus to give proper conditions of attachment and food. Obviously, if the tendency to regenerate abnormally, as in cancer, were dominant over the tendency to regenerate normally, very little would remain in the organic world but cancerous individuals.

Similar inoculation experiments carried out on mice by Loeb and Fleisher,[9] although differing in details, agreed with Little and Tyzzer's work in essentials, that is, susceptibility to the implant occurred in the first hybrid generation, showing the presence of a dominant concerned in the susceptibility; and the method of inheritance in later generations indicated a multiple factor. Obviously, since the tendency to regenerate normally is dominant over the tendency to regenerate abnormally, all genetic studies with grafted tumors, must, if the technic is accurate, show susceptibility to inoculation in the first hybrid generation of susceptible strains.

The fundamental basis of susceptibility to grafts, then, is the exact opposite of the fundamental basis of susceptibility to spontaneous cancer, which is the tendency of the assaulted tissues to regenerate abnormally in the uncontrolled and undifferentiated method of the neoplasm.

III. SPONTANEOUS TUMORS

Prior to the year 1910 most of the work in cancer research had been done with grafted tumors. The relative ease with which this grafted material was procured, and the extreme difficulty of securing a stock of animals with spontaneous cancer, naturally led to the selection by practically all workers of the easily secured material. As has already been pointed out, a grafted tumor is in the nature of a parasite growing in a foreign host. It is the cells of the graft that proliferate, not the cells of the host. A spontaneous neoplasm is the result of the cell proliferation of the tissues of the animal itself, and is the outcome of its own metab-

9. Centralbl. f. Bakteriol. u. Parasit. **57**: 135, 1912.

olism. Its fundamental biology, therefore, must in all its ramifications be different from that of a grafted tumor.

The material used for the studies carried on in this laboratory has been fully described in previous publications.

As the results of this work have been serially published for the last ten years with masses of exact data and genealogical charts,[10] I shall only summarize certain of those results here.

INHERITANCE OF SPONTANEOUS NEOPLASMS

The inheritance behavior of spontaneous neoplasms is opposite from that of grafted tumors. Contrary to the behavior of grafted tumors in heredity, which has been shown to involve multiple factors, the main factor being a dominant or the ability of the assaulted tissues to regenerate normally, the inheritance behavior of spontaneous cancer has uniformly been that of a simple Mendelian recessive, throughout the entire results obtained in this laboratory. The immediate basis of spontaneous tumors is the tendency of the tissues to regenerate abnormally to assaults of various kinds, that is, to chronic or acute irritations, and this tendency to regenerate abnormally has uniformly behaved like a recessive unit character, in matings between analyzed pure cancerous and pure noncancerous individuals.

Throughout the hundreds of matings made in this laboratory, between analyzed cancerous and noncancerous mice, the cancer tendency has never in a single instance appeared in the first hybrid generation. This shows conclusively that susceptibility to spontaneous cancer cannot be dominant over resistance to cancer. Here, in this basic difference between susceptibility to grafted tumors, and susceptibility to spontaneous cancer, we have the explanation of the different results obtained by students of cancer heredity working with grafts, and those working with spontaneous neoplasms. In both types of studies the tendency to regenerate normally has uniformly been shown to be dominant over the tendency to regenerate abnormally.

10. J. Cancer Res. **7**: 146, 1922.

IV. EXPERIMENTAL LIVER SARCOMA IN RATS

There is now under way in the Crocker Research Fund Laboratory the experimental production of liver sarcoma in rats, by the feeding of the larval stage of the tapeworm of the cat. Bullock and Curtis [11] in 1920 reported as follows:

There were 1,165 original rats fed with a suspension of tapeworm eggs, ten to sixty eggs to the drop, 1 or 2 drops being given each rat. Six hundred rats were killed five months after feeding, none of them showing any tumor; 565 of these experimental rats then remained alive. Of these 565 rats, 230 were killed or dead fifteen months after the original feeding. Fifty-five of them showed liver sarcoma, i. e., 510 of them did not develop liver sarcoma in fifteen months.

Two thousand five hundred descendants of the original rats were added to the experiment, making a total of 3,665. Thirty of the first generation descendants also showed liver tumor, making a total of eighty-five that had liver sarcoma out of 3,665 rats fed with tapeworm eggs. Of the rats thus fed, 3,580 did not develop liver sarcoma.

The authors state that young rats of certain strains seemed most likely to produce these experimental liver tumors. They further state that most of the tumors undoubtedly arose in the walls of parasitic cysts, and that the others were probably of the same origin.

The authors do not state whether tapeworms were found elsewhere than in the liver in larval stage. None of these rats is reported to have shown tumors in any other location except in the liver and regional metastases.

They state that certain strains are more susceptible than others, and at the 1923 meeting of the American Association for Cancer Research, Wood reported that when rats that developed liver sarcoma were bred together, much higher rates were obtained in the offspring, such families sometimes giving 100 per cent. of positive results. This shows a most striking hereditary basis underlying the success of this experiment.

11. Proc. New York Path. Soc. **20**: 6-8, 1920.

It is of interest also to note, that in an article concerning "a transplantable myosarcoma" of the rat,[12] Bullock and Curtis report a spontaneous tumor of this type occurring in the tail of a rat which had been infested with tapeworm larvae without developing a liver sarcoma, thus showing that this rat developed the type of tumor to which it was predisposed rather than the type of tumor experimentally attempted.

PATHOLOGIC CONDITIONS RESULTING FROM NATURALLY INGESTED TAPEWORM

Every effort has constantly been made in this laboratory to exterminate all vermin and parasites, such as lice, flies, bedbugs, cockroaches, tapeworms and nematodes, and the more perfectly these parasites are eliminated, the higher is the spontaneous tumor rate. In spite of these constant efforts, there have been periods when the stock has shown both tapeworms and nematodes, notably when local tramp house mice and wild Norway rats have been carrying the same types of parasitic worms.

Among the 43,984 necropsies performed in this laboratory to date, there have been 1,600 cases of tapeworm naturally ingested. Among these 1,600 mice with tapeworm, there have been 157 with tumors, leukemia or pseudoleukemia. The tumors in mice with both tapeworm and neoplasms were distributed as follows:

Mammary gland, 101: 95 carcinomas, 3 sarcomas, 3 adenomas.
Lungs, 32 adenomas and adenocarcinomas.
Liver, 4 adenomas; 3 had no worm cyst in liver; 1 had no adjacent cyst in liver.
Ovary, 1 adenoma.
Prostate, 1 sarcoma.
Preputial gland, 1 adenoma.
Testicle, 2: 1 carcinoma of 6 nodules, 1 mesothelioma.
Jaw, 3 squamous cell carcinomas.
Thymus, 2 lymphosarcomas.
Retroperitoneal tissues, 1 lymphosarcoma.
Spinal column, 1 myeloma.
Stomach, 1 sarcoma.
Mouth, 1 sarcoma (at site of wound).
Eyelids, 1 squamous cell carcinoma.

12. J. Cancer Res. **7**: 3, 1922.

Leg, 1 osteosarcoma (point of fracture).
Hip bone, 1 osteosarcoma (point of fracture).
Pancreas, 1 carcinoma.
Duodenum, 1 carcinoma.
Head, 1 squamous cell carcinoma. Total, 157.
Leukemia, 5; Pseudo Leukemia 7; Grand total 169 tumors, leukemia and pseudoleukemia.

There is no reason to suppose that the four liver adenomas were caused by tapeworm any more than the other 165 neoplasms in infested mice, since in three of the cases there was no worm cyst in the liver, adult worms being in the intestine and common bile duct; while in the single case of liver adenoma where there was a liver cyst, the walls of this cyst showed no proliferation whatever, and the adenoma was in a different lobe of the liver with no cyst in that lobe.

On the negative side the evidence is still more striking. There were 1,695 cases of liver parasites that did not produce liver tumor even in strains which normally produce 50 per cent. liver tumor incidence. The mice in these 50 per cent. liver tumor strains which had liver tumor did not have tapeworm, and the mice in these strains that had tapeworm did not have liver tumors.

Only 157 of about 5,000 spontaneous neoplasms in this stock were in mice infested with tapeworm. That is, about 97 per cent. of these neoplasms occurred in mice not infested, making it beyond dispute that the origin of neoplasms is in no way dependent on the presence of tapeworm.

There is a perfectly standard result of the normal ingestion of tapeworm, as shown by necropsies in this laboratory, and it does not involve neoplastic proliferation in the liver or elsewhere either in the mice of tumor strains or in mice of nontumor strains, but instead the results are of a highly degenerative character.

It is interesting also to note that the wild house mice, the wild Norway rats and the Albino rats necropsied in this laboratory, which have had tapeworm, have shown exactly the same types of pathologic changes shown by the mice in this laboratory.

As stated in a previous article,[13] complicating diseases such as tapeworms and nematodes in the digestive tract or any other highly destructive disease, greatly retards spontaneous tumor growth. For example, if we compare tumorous mice (after they have ceased reproducing), these mice all being from the same or allied strains and of about the same age, we get some interesting facts. We find that mice without tapeworm, nematodes or any other highly destructive disease, grow on an average nearly twenty-five times as much tumor daily as do mice infested with tapeworms or other highly destructive parasites. In the experience of this laboratory, then, instead of causing tumor growth in the liver or elsewhere, the infestation of mice by tapeworms or nematodes, etc., greatly retards the growth of such tumors as the animal develops.

The difference between the pathologic findings in the Bullock and Curtis experiment of artificial feeding with tapeworm eggs, and those in this laboratory from normally ingested tapeworm, are certainly striking. Whereas, they report a considerable percentage of liver sarcomas arising in the walls of cysts containing live tapeworm larvae, and do not report any degenerative changes, as the result of this feeding, the findings in this laboratory are exactly opposite, namely, no liver sarcomas or other neoplasms traceable in any way to tapeworm larvae, no proliferation of any sort in the cyst walls containing either living or dead larvae, and the most extensive degenerative changes causing death, as the result of naturally ingested tapeworm eggs. Moreover, 122 of the total 126 liver tumors arose in mice which had no tapeworm or any other discoverable parasite.

There are two suggestions which may throw some light on these apparently widely divergent results from the ingestion of tapeworm eggs:

1. Bullock and Curtis evidently did not make any biologic analysis of the stocks used in their experiment, in order to determine what percentage of these rats would produce liver tumor without the ingestion of tapeworm eggs. That there was a biologic difference

13. J. Cancer Res. **5**: 5, 1920.

in the various strains in the matter of tumor production, is shown by the different percentages of tumors arising in the different strains used, and also the difference in the formation of lung metastases among the different strains.

2. If we assume that all of these liver sarcomas in rats were due only to the irritation of tapeworm larvae on the walls of the cysts, there remains a synthetic suggestion which will correlate their results and mine.

Bullock and Curtis state that all the tumor bearing rats presented multiple cysts in the liver, varying from six to eighty-four in number. Obviously the rats whose livers contained eighty-four larval cysts must have swallowed at least eighty-four eggs. No mouse has ever been found in this laboratory with more than five tapeworms or larvae. The relatively few tapeworm eggs normally ingested by mice in this laboratory or by the wild rats and wild house mice which I have necropsied, apparently did not produce an irritating effect of the type to overthrow their normal regenerative powers in the tissues of the liver, even in the strains subject to 50 per cent. of spontaneous liver neoplasms, but instead produced a violent effect sufficient to cause fatal degenerative changes, with no opportunity for proliferation of any sort.

Whereas, the sixty to eighty-four experimentally fed tapeworm eggs (assuming that the irritation from the larvae was in every case the certain cause of the proliferation) apparently were efficient in producing an irritation in eighty-five rats capable of overthrowing their normal regenerative powers in the tissues of the liver and not sufficient to cause fatal degenerative changes. It is, however, difficult to see why, as Bullock and Curtis state, only one of these cysts usually showed proliferation, if the irritation of the cyst content was the efficient cause.

Even if it should prove to be possible to cause liver sarcoma in every animal by the ingestion of tapeworm eggs, this would not disprove the inheritability of cancer, for note the biologic facts.

There resides in every living organism the power to regenerate within certain limits. These limits are set

by the normal metabolism of the organism. For example, under normal conditions a beheaded planarian can regenerate a head. But if this beheaded worm is put into a solution of alcohol, not lethal in strength, it is no longer able to regenerate a head, but will perform partial regeneration in proportion to the strength of the alcohol solution. If the solution is sufficiently strong all power of regeneration is lost.

If sea urchin eggs are centrifuged, they will not generate normally. If the centrifuging is sufficient, they will not generate at all. A less degree of centrifuging will produce abnormalities of generation, proportionate to the degree of centrifuging used.

These facts demonstrate that it is possible to overthrow partially and even completely, not only the normal inherited regenerative powers in the tissues of an organism, but even the normal inherited generative powers. There is no organic mechanism which cannot be overthrown wholly or in part, by a sufficiently strong assault. For example: it is possible by a sufficient assault, to destroy the pigment making mechanism in a young mouse with inherited black hair, and thus cause local albinism at the point of assault. But this fact has nothing to do with the inherited pigment making function or its potentialities under normal conditions.

A parallelism to these facts of normal regeneration and generation, and the possibility of their destruction partial or complete, undoubtedly exists in the facts of abnormal regeneration operating in the production of neoplasms. Resistance to neoplasms has consistently behaved like the presence of a mechanism fitted to control proliferation and differentiation in regenerative processes. This mechanism, like the pigment making mechanism, it is undoubtedly possible to kill; so that by an efficient assault it might be possible to produce a local lack of this mechanism, just as we can produce local albinism by an assault upon the local and inherited pigment making mechanism.

Again: the pigment-making mechanism exists in different degrees among different individuals, so that among mice, for example, some individuals form red

pigment (most highly oxidized melanin); some individuals form gray pigment (a less degree of oxidation of melanin); some individuals form black pigment (a still less highly oxidized melanin); and so on, down to those individuals whose pigment making mechanism is of the type which produces only the palest blue or cream color, the latter being barely distinguishable from albinic white.

In just this way, individuals may vary greatly in the degree of their mechanism for controlling growth and differentiation in regenerative processes, i. e., the cancer resistant mechanism. Individuals of the first class, who have the highest degree of noncancer mechanism, would then rarely produce cancer under any provocation. But individuals with the lowest degree of cancer resistant mechanism, might relatively easily succumb to artificial conditions for cancer production. Whereas, under the normal life of the organism, no set of circumstances would arise that could produce cancer, under the continued and artificially excessive provocation they might succumb; just as an individual with enormous muscular power, capable of resisting any normal impact against his musculature, would succumb under the impact of 100 tons. His mechanism, efficient under normal conditions, would have no opportunity to function. Many of the experimental procedures using artificial means of producing tumors, may easily be of this shattering type. So that, in those individuals that have only a low degree of cancer resistant mechanism, this controlling mechanism may have no opportunity to function.

However, none of the stocks used for the experimental production of cancer, so far reported, has ever been analyzed as to its natural cancer potentiality, and therefore we have no scientific basis for decision as to what part of the results of such experiments are due to natural cancer potentiality and what portion remains the unquestioned experimental result.

It might then be possible, by a violence sufficient to destroy the cancer resistant mechanism, to cause cancer in every organism, the readiness with which this could

be done being dependent on the degree of cancer resistant mechanism possessed by each individual.

It may, therefore, be possible to discover a type or types of irritation sufficient to cause neoplasms in every living organisms, and tapeworm larvae, nematodes, coal tar painting and roentgen-ray burns, along with other types of irritation, may any or all of them prove to be efficient causes for the overthrow of inherited cancer resistant mechanism, just as all heads can be turned gray or even cut off, no matter what the inherited potentialities might be; for one inherited potentiality of every organic mechanism is that it can be destroyed by some form of assault. The inherited mechanism for cancer resistance, therefore, would not differ in this respect from every other inherited potentiality; that is, it undoubtedly can be destroyed.

The reverse also may prove to be possible. Susceptibility to cancer has consistently behaved like the absence of a mechanism fitted to control proliferation and differentiation in regenerative processes. If this absence should prove to be systemic it might be possible so to stimulate the defective center as to cause it to function at least with partial efficiency, as a defective pancreas can be fed with insulin. If the defective mechanism should prove to be local it might prove to be possible to implant a local mechanism either physical or chemical.

Biologically, therefore, cancer therapy must be one of two sorts: either the removal or destruction by surgery, radium, roentgen ray or other destructive agents, of the local tissues lacking the mechanism for resistance, or the finding of a defective local or systemic center for resistance to cancer which by artificial stimulation can be made to function efficiently, at least temporarily, in the control of regeneration. The heredity behavior of cancer, however, has consistently been that of a local lack of mechanism, since susceptibility to tumors of specific tissue in specific organs is inheritable, and strains of mice never showing mammary gland carcinoma, produce 100 per cent. lung tumors, etc. This fact argues a local rather than a systemic lack of mechanism.

VI. THE ARTIFICIAL PRODUCTION OF SPIROPTERA CARCINOMA IN RATS AND MICE

Fibiger states that he produced fifty-four squamous cell carcinomas in the digestive tract [14] in 116 rats fed with nematode larvae. Also in experiments, possibly still under way, he had at the time of publication observed three cases of carcinoma in the fundus of the stomach of white mice [15] fed in exactly the same way on these larvae.

Fibiger's reports show that there is difference in susceptibility among different strains which he tested, thus showing an underlying hereditary basis for this susceptibility, and that mice seem very much less susceptible than rats to this type of experimental neoplastic production, thus showing a racial heredity tendency underlying this susceptibility.

In his report No. 5 [16] he sets forth the difficulties he experienced in producing any experimental spiroptera cancer in mice, finally succeeding in securing only three such cases among hundreds of mice tested. He also states that he did not succeed in any case in producing spiroptera cancer in wild mus musculus, mus sylvaticus, or wild Norway rats (mus decumanus). He is forced to conclude from these negative results that there probably must be a predisposition to spiroptera cancer determining the success or failure of this experiment both for different species and for different individuals.

Such an explanation of his results places them in perfect harmony with the fundamental influence of heredity in cancer susceptibility, observed and reported by this laboratory for the last twelve years. It is in complete conflict with the conclusions hastily reached by some scientists from Fibiger's early reports, that spiroptera carried a cancer germ, or was in some other way an essential agent in the causation of cancer.

Fibiger further states that spontaneous mammary gland carcinoma and mammary gland sarcoma have arisen in mice whose stomachs he had infested with spiroptera without securing stomach neoplasms.

14. Det. Dgl. Scl. Biol. Med. **17**, 1918.
15. Det. Vid. Scl. Biol. Med. **22**: 1918.
16. Det. Vid. Scl. Biol. Med. **1**: 11, 1918.

This result is in harmony with the results in this laboratory of nematode infested mice, which instead of tumors in the digestive tract develop tumors in the mammary gland, lung, liver, retroperitoneal tissues, etc., in accordance with their inherited potentiality and irrespective of nematode infestation.

That is, the presence of artificially introduced larvae in the liver or stomach and intestines of rats and mice of spontaneous cancer strains, does not produce neoplasms in the liver or stomach or intestines necessarily, but spontaneous neoplasms arise in those organs which by inheritance lack the cancer resistant mechanism, just as they do in this laboratory whether or not mice have normally ingested nematodes.

It is extremely interesting and gratifying to find this striking harmony between the experimental spiroptera and liver sarcoma and spontaneous neoplasms in mice, whereby the demonstration of the inheritability of spontaneous cancer is corroborated by a line of work which seemed at first (to many) likely to show that experimental cancer could be produced at will in all animals, and which was taken by many commentators to indicate that the tendency to cancer might not, after all, be inheritable. These results lead us to hope that when the field of experimental cancer production has been more completely investigated, the most perfect harmony will be found to exist in every detail between such lines of work which experimentally produce true neoplasms, and the work with spontaneous cancer.

VII. PATHOLOGIC CHANGES FOLLOWING THE NORMAL INGESTION OF SPIROPTERA

There have been to date in this stock sixty-one cases of nematode infestation from normally ingested larvae. Among these sixty-one mice there have been ten with tumors and one with leukemia. There have, therefore, been fifty mice infested with nematodes, which have not shown neoplasms anywhere, nor have they shown leukemia or pseudoleukemia.

The tumors in mice with both nematodes and neoplasms, were distributed as follows:

Mammary gland, 6 carcinomas.

Lung, 2: 1 carcinoma, 1 carcinoma and 1 adenoma.
Liver, 1 adenoma.
Retroperitoneal, 1 lymphosarcoma.
Leukemia, 1. Total 11 tumors and leukemia.

None of these mice infested with nematodes had tumors in the stomach or intestine or in the mouth or tongue.

On the negative side, the evidence is still more striking. Of the 5,000 spontaneous tumors arising in this stock to date, only ten were in mice infested with nematodes. There have been to date, only thirteen cases of neoplasms in the gastro-intestinal tract, among the mice in this laboratory. Of these, not one occurred in an animal infested with nematodes, tapeworm or any other discoverable parasite. Moreover, some of the mice with nematodes in the stomach were members of the strains carrying the few spontaneous stomach and intestinal tumors which have occurred in this stock.

There is a perfectly standard result of the normal ingestion of nematodes as shown by necropsies in this laboratory. These results are of a highly degenerative character and do not involve neoplastic proliferation in the gastro-intestinal tract or elsewhere, either in the tumor strains or in the non-tumor strains, not even in the tumor strains where the stomach and intestinal tumors have arisen.

It is interesting to note here, as in the case of tapeworm infested mice, that the wild house mice and wild rats necropsied in this laboratory, show exactly the same types of pathologic changes where they are infested with nematodes, as do the mice belonging to this stock.

Fibiger's results, in failing to obtain spiroptera cancer in wild mus musculus, mus sylvaticus and mus decumanus, even by the injection of 800 larvae into the stomach at one time, is in beautiful harmony with these results obtained in this laboratory.

Two striking differences emerge in the results of artificial and of naturally ingested nematode larvae: 1. Fibiger states that young rats and mice seem more susceptible than older animals. Bullock and Curtis make the same statement with reference to their experi-

mental liver sarcoma. The reverse is true of spontaneous neoplasms both in rodents and in man. 2. Fibiger injected 300 to 800 larvae into each of his animals. The highest number of nematodes ever found in an animal necropsied in this laboratory was eleven in a wild house mouse. The average was four or five. Many of the animals had only one worm, and some of them two or three. Where the larger number of larvae had been swallowed, they were not ingested at the same time, as the worms were in different stages of development.

Evidently this smaller number of worms does not furnish irritation of the type to overthrow the cancer resistant mechanism, even in the stomach tumor strains, although even one worm is sufficient to cause fatal degenerative changes.

Assuming the nematodes to be the efficient cause of stomach cancer in all of Fibiger's cases, 300 to 800 worms would then be of the type to destroy the non-cancer mechanism in fifty-four rats and of three of the laboratory mice tested; but would not be of the type to destroy the cancer resistant mechanism in most of the laboratory rats, all but three of the laboratory mice, and all of the wild rats and mice tested by Fibiger, just as the lower number of from one to eleven worms found in the laboratory mice in this stock, and all of the wild rats and mice of this vicinity necropsied, were not the type of irritation fitted to overthrow the cancer resistant mechanism.

When this whole field of experimentally produced cancer has been thoroughly worked over, *we shall probably find that predisposition to the type of tumor produced is the one fundamental essential, just as it is the one fundamental essential in spontaneous neoplasms.* Fibiger's meager results in securing spiroptera cancer in mice, even in mice of spontaneous cancer tendency, is in very strong corroboration of the hereditary nature of cancer.

We seem to have here, in this possibility of the overthrow of the cancer resistant mechanism, a parallel with other cases of the overthrow of regenerative powers, for example, the power of the skin to regen-

erate a certain amount of burned area, but its overthrow in the presence of a larger burned area. Undoubtedly, there is here also an underlying hereditary tendency to the capacity to regenerate a greater or a less amount of destroyed skin.

This difference in the reaction to naturally ingested worms numbering from one to eleven, and artificially injected worms numbering from 300 to 800, seems further to corroborate the theory that cancer tendency is due to the lack of a mechanism fitted to control proliferation and differentiation in regenerative processes. Apparently 300 to 800 worms is sometimes efficient in overthrowing this mechanism in some animals, probably in exact accordance with their inherited potentialities; although there is no evidence in Fibiger's reports that these same rats might not have developed gastric tumor from other causes than spiroptera; that is, they may have lacked the cancer resistant mechanism in the stomach. That wild rats have been found showing stomach tumors where they had ingested nematodes and others where they had not ingested nematodes, would indicate that rats are normally more susceptible to stomach tumors than are mice. This is another indication of the racial hereditary tendency underlying the development of neoplasms.

From one to eleven worms have never to date been found efficient in overthrowing this mechanism, even in mice of gastric tumor strains; but if worms were the host of a specific cancer germ, one to eleven worms should be sufficient to introduce the germ.

The essential fundamental in which the artificial production of tumors differs from the spontaneous production of neoplasms, is that in the former case the experimenter destroys the normal metabolism of his animals by the violence of his methods of irritation, exactly as the pigment making mechanism can be destroyed by a blow on the head. He is not, therefore, testing the behavior potentialities of his experimental animals in normal conditions. This violently destructive method of irritation, which overthrows such cancer resistant mechanism as the attacked animal organ may possess, may very probably at the same time overthrow

other metabolic mechanisms and relations on which we might depend in a cancer therapy. That a much more wholesale destruction of cancer resistant mechanism is effected in these experiments, than obtains in spontaneous cancer, is shown by the vastly greater extent, for example, of Bullock and Curtis' experimental liver sarcoma, than has occurred in any case of spontaneous liver tumors of any type, in this laboratory.

In my opinion Fibiger's results show that there is an inherited difference in the stability of this mechanism and the amount of violence necessary to overthrow it, in different races, different strains, and even in different individuals of the same strain; and his results justify the conclusion that there are some individuals, some strains, and even some whole races, in which the cancer resistant mechanism cannot be overthrown by any violence short of fatal violence. Bullock and Curtis are evidently finding the same to be true of their experimental liver sarcoma.

VIII. TAR CANCERS

The first successful experimental production of tar cancer was reported by Yamagiwa and Ichikawa [17] in 1915. Later Tsutsui [18] produced the same type of cancer in mice, and Fibiger, and Fibiger and Bang [19] have obtained many such cancers in mice.

The infrequency of metastasis from these tar cancers is in harmony with the behavior of spontaneous squamous cell carcinomas of mice arising in this stock, which seldom produce metastasis, and also in harmony with the tar cancers produced by Yamagiwa in the ears of rabbits, which seldom showed metastasis.

IX. SPONTANEOUS SQUAMOUS CELL CARCINOMAS IN MICE

Among 40,370 necropsies performed in this laboratory, and given careful microscopic examination, 191 spontaneous squamous and basal cell carcinomas have occurred, none of them due to exposure to coal-tar

17. Mittheil. der Med. Fak. Univ. Tokyo **15**, 1915, 1917, **19**: 1918; J. Cancer Res. **3**: 1918.
18. Ztschr. f. Krebsforsch. **12**: 2, 1918.
19. Det. Kgl. Vid. Scl. Biol. Med. **3**: 4, 1921.

products of any sort. The location of these tumors was as follows:

Face including muzzle, skin, and eyelids, mouth, ears, trunk, 100; mammary gland, 65; lower jaw, 15; stomach, 5; rectum, 2; vulva, 2; vagina, 1; lung, 1. Total, 191.

Over 200 of these squamous cell carcinomas have occurred to date, but only those whose clinical diagnosis has been confirmed by microscopic study are included in this report.

Nearly all the tumors arising on the head and trunk were located at the site of a healed wound, often beneath the scar tissue. The tumors of the jaw and mouth apparently resulted in many instances from the irritation of broken or irregular teeth. The carcinomas of the muzzle skin were almost uniformly founded on a chronic and constantly scratched dermatitis.

The number of metastasizing tumors obtained by painting with coal tar is greater than from these spontaneous squamous tumors; another indication of the greater violence of the experimental method, and the more widespread overthrow of the cancer resistant mechanism.

Fibiger's notable failure to produce more than three spiroptera cancers in the stomachs of mice, has caused him to throw most of his efforts recently toward producing tar cancers of the skin in mice. His reports, issued in 1921 on this work, is favorable to such experimental cancer production.

When he has followed this line of experiment with the same care, the same length of time, and the same diversity of animal subjects of the experimentation which he used in his spiroptera experiments, he will doubtless find that here also the essential fundamental factor necessary to cancer production of this sort, is the hereditary predisposition of the animal, and of the race, to the kind of cancer attempted. The beautiful harmony between his results in spiroptera cancer, and the spontaneous stomach and intestinal cancers in this stock, will then probably be duplicated by a similar harmony between his results in experimental tar cancer, and the spontaneous squamous cell carcinomas of the

skin, *arising from various types of chronic irritations,* in this stock.

The mouse is rather susceptible to squamous cell carcinomas of the skin. It is probable that in any set of laboratory mice procurable on the market, a large number will by heredity be predisposed to squamous cell cancers of the skin. More success in producing skin cancers experimentally in mice either by coal tar products or by many other possible methods, may therefore, confidently be looked for, than stomach and intestinal cancers, which are rare in mice.

The longer these experiments in the experimental production of cancer are carried on, and the more thoroughly they are tested out, the more certainly and completely (in the opinion of the author) will they be found to harmonize with the fundamental facts of spontaneous cancer, when the tumors produced are true neoplasms. *Since heredity is a certain and fundamental underlying factor in the occurrence of spontaneous cancer, it must inevitably in every case of true experimental cancer of the tissues of the animal itself, also be found to be a certain fundamental factor.*

A synthetic consideration, then, of the results so far obtained in the experimental production of cancer, and in the spontaneous production of cancer, shows a striking harmony between these two in all fundamentals.

Along with these encouraging harmonies in fundamentals, there are also fundamental differences, and the probable overthrow of other normal and probably vital mechanisms by the same experimental violence which overthrows the cancer resistant mechanism, must be taken into consideration in all conclusions regarding the etiology of cancer, and all cancer therapy.

It has been stated that probably no two spontaneous tumors are identical in structure, and that grafted tumors can teach us many things better than spontaneous tumors can, because the implants are structurally identical with the original tumor. This argument of the microscopist might possibly be put forth regarding all other experimental tumors of a given type, that is, they would probably be very similar to one another. There is no doubt, however, that all

spontaneous neoplasms of a given type and of a given organ, are identical in fundamentals, and differ only in minutiae. This possible divergence in minutiae should not interfere with our learning from them, just as we can learn the fundamentals concerning the structure and biologic behavior of any organic entity, although no two of any given organism, or any given organ, are identical.

It seems far more essential that the metabolic conditions surrounding the origin and progress of the tumor, should be the fundamental inherent conditions of the animal's tissues, as they are in spontaneous neoplasms, and not altered as they must be by experimentally produced tumors, rather than that the minutiae of tumor types should be identical. The alteration of the metabolic conditions surrounding the experimental tumor seems to the author to be a serious handicap both in the study of the etiology of tumors and of cancer therapy.

It remains to be seen whether or not it is possible so to strengthen the hereditary cancer resistance, that is, to strengthen the normal regenerative power, that it is impossible to overthrow it. That is, is it possible, by the right selective breeding, to evolve a strain whose normal regenerative powers cannot be overthrown by the most violent or long continued irritation, even of the experimental type (short of fatal violence)?

It remains also to be seen whether or not it is possible to insinuate into the metabolism an increased stability of normal regenerative power and consequent cancer resistance.

In the light of our present knowledge of cancer, this would seem be be the most hopeful preventive method in the treatment of individuals of known inherited cancer tendency.

SUMMARY

1. Certain fundamental harmonies and certain fundamental differences exist between spontaneous neoplasms and all artificially produced tumors.

2. The essential harmony in all these is the fact that all tumors, both spontaneous and experimental, have been shown to depend fundamentally on the inherited predisposition of the animal's tissues.

(*a*) In grafted tumors, the success of the experiment *depends fundamentally upon the inherited tendency of the animal's tissues to regenerate normally* and furnish proper conditions of attachment and food, instead of abnormally as is the case in spontaneous cancer.

(*b*) In liver, stomach and intestinal tumors resulting from parasitic infestation, *the success of the experiment depends on the inherited tendency of the animal's tissues to attempt regeneration under such irritation,* and the violence of the method which overthrows such normal regenerative powers as the animal's tissues may possess. Many animals and many strains thus far tested, both by artificially introduced and by naturally ingested parasites, have been unable to regenerate the irritated tissues either normally or abnormally, and their organs have merely gone to pieces in degenerative changes.

(*c*) From tar painting, the same type of squamous cell carcinomas of the skin arise, as arise spontaneously from similar chronic skin lesions in mice produced by many other causes, and in all probability when this type of experiment has been thoroughly tested out, it will be found to depend on the inherited tendency to skin carcinoma, which could equally well be produced by other types of chronic attacks on a susceptible skin.

3. The fundamental difference between spontaneous neoplasms and all artificially produced tumors, seems to be that the spontaneous tumor is the product of the animal's own inherent metabolism, that is, the inherited tendency to regenerate abnormally under various assaults on the tissues; while, to date, all experimentally produced tumors seem to indicate that the violence of the method may have overthrown inherent cancer resistant mechanisms, with the probability at the same time of the overthrow of other vital fundamental metabolic mechanisms.

4. These harmonies between spontaneous and artificially produced tumors give promise that it may be possible to strengthen the cancer resistant mechanism, since there seem to be varied grades of such resistant

mechanisms, and there are evidently resistant mechanisms that cannot be overthrown by the most violent and long continued methods yet attempted.

Dec. 10, 1923.

ISOLATION OF DUCREY BACILLUS FROM THE SMEGMA OF THIRTY MEN *

JULIUS BRAMS

SUMMARY

A gram-negative streptobacillus having the morphologic and cultural characteristics of the Ducrey bacillus was isolated in pure culture from the smegma of normal men.

The organism was recovered from five of thirty men examined.

The isolation of this organism from normal men may explain many heretofore unknown phases of chancroidal infection.

Feb. 11, 1924.

LYMPH ENDOTHELIOMA OF THE DUODENUM; HEMANGIOMA OF THE INTESTINE; LYMPHOBLASTOMA OF THE STOMACH

LEON BLOCH

Case 1.—Miss C. L., aged 19, came for examination on Sept. 21, 1923, complaining of symptoms indicative of a chronic severe anemia, such as pallor, shortness of breath, weakness and occasional edema of ankles. At the age of 7 she lost a considerable amount of blood through biting a small vascular tumor under her tongue, remnants of which still persist. On and off since then the symptoms of anemia

* Complete paper published in The Journal of the American Medical Association, April 12, 1924, p. 1166.

have recurred at various times in a varying form, necessitating her being withdrawn from school at one time, and at another taking a trip to California to recuperate.

The family history, is negative. She had scarlet fever at 6. The vascular tumor, above referred to, was ligated at the age of 7 and has given no trouble since. Aside from a pronounced pallor, a soft basal systolic murmur, a barely palpable spleen, and a slight edema of the ankles, the physical examination was negative.

The urine gave a positive indican reaction. The blood revealed a 19 per cent. hemoglobin. Red blood corpuscles, 1,860,000; white blood corpuscles, 8,000; differential: polymorphonuclears, 65 per cent.; small lymphocytes, 14 per cent.; large lymphocytes 17 per cent.; transitionals, 4 per cent. Anisocytosis and poikilocytosis. Stool examination yielded a very intensely positive Benzidine and Guaiac test continuously with the patient on a meat free diet. Stools were intensely black and hard. She entered the Michael Reese Hospital, September 28, and was placed on a high caloric soft diet. As there was no improvement, October 6 a transfusion of 600 c.c. of blood was made by Dr. A. A. Strauss, following which the hemoglobin reached 49 per cent. At this time a complete gastro-intestinal roentgen-ray examination was carried out with the result that a small defect on the pyloric end of the lesser curvature margin of the duodenal bulb was discovered. In the absence of any typical ulcer symptoms the diagnosis rested between a benign tumor of the duodenum and a duodenal ulcer. As ulcer management led to no improvement and the hemoglobin sank to 30 per cent. an exploratory operation preceded by another transfusion was performed by Dr. A. A. Strauss. This revealed a small nodule on the duodenum, not typically ulcer in character, and on excision and examination proved to be a very small lymph endothelioma of the duodenum.

Subsequently, for about a week the stools showed less blood, and for about two or three days no blood, but a few days later the blood reappeared, the hemoglobin sank and November 22 a second operation was decided on, this time on a diagnosis of bleeding tumor of the bowel, probably the small intestine. Operation revealed a small, cherry-sized nodular pedunculated tumor at the head of an intussusception 5 inches in length and about 14 feet from the pylorus. Above this lesion the bowel was empty and pink; below, full of blood and purplish. No other tumor was found either in small or large intestine. This was removed and on histologic examination proved to be a hemangioma.

The subsequent course was uneventful, and when last seen, Feb. 11, 1924, the patient showed a hemoglobin of 88 per cent. Throughout the whole course the temperature ranged from 98 to 99 F., except after transfusion when it reached 102 F. After the second operation the temperature was normal and remained so.

The following is a report of the pathological condition, from the pathological department of the hospital by Drs. O. T. Schultz and Bernard Portis: The first specimen removed was $1 \times 0.5 \times 0.5$ cm., with a depressed center and apparently ulcerated surface. The surface epithelium was intact, beneath which was a well defined layer of Brunners' glands. Displacing the glandular layer and lying in the submucosa is a new growth, consisting of a lobulated cellular structure, the cells of which are chiefly spindle shaped and forming anastomosing cords about a central connective tissue structure. This tumor mass is well encapsulated throughout its entire extent, and although it compresses the normal tissue, it does not invade it. The diagnosis made was lymphendothelioma or misplaced fetal tissue, which has produced a small growth.

The second specimen on gross examination measured $2 \times 1.6 \times 8$ cm. The cut surface shows a trabeculated structure situated beneath the mucosa and filled with a dark material.

Microscopic examination shows an intact mucosa which contains a few dilated blood vessels. The submucosa contains a cavernous hemangioma, in which the blood spaces are quite large. The walls are thickened, fibrotic and hyalinized. There is some thrombosis of the vascular spaces, a few of which contain calcium deposits. This growth in addition involves the muscularis, which layer is poorly defined. There is no evidence of malignancy.

Including three of four cases of hemangioma of the stomach, reported by Judd and Rankin,[1] I have found records of twenty-six cases of hemangioma of the gastro-intestinal tract reported in the literature. There are undoubtedly many more cases reported.

The first one is by La Boulbene, in 1872, and quoted by N. G. McCallum.[2] In no instance was a diagnosis of the condition made, although in one of the four cases reported by Judd and Rankin a benign tumor of the duodenum was diagnosed, in another benign tumor

1. Judd, E. S., and Rankin, F. W.: Ann. Surg. **76**: 28, 1922.
2. McCallum, W. G.: Bull. Johns Hopkins Hosp. **17**: 185.

of the stomach and in the other two malignant disease was the diagnosis. In the present case, a benign tumor of the duodenum was considered, in the first instance, and a hemangioma of the bowel was considered, only because of the attention attracted to this condition being a possibility as a result of the perusal of the literature.

In many instances the tumor was a cause of other symptoms, as obstruction, or was found as an accidental accompaniment of operation, or postmortem, or as a cause of death from hemorrhage supposedly due to duodenal ulcer location,—small, or large bowel, rectum.

There are several opinions as to the origin of hemangioma. All are more or less agreed that they are either congenital, or develop as Virchow has it, from sprouts appearing first in the site of preexisting blood vessels. The tumor is a proliferating one, caused by an irritation and leading ultimately to a rich mass of connective tissue.

Thoma assigns a mechanical factor to their origin, increased blood pressure, loss of vascular support and aided by rapidity of blood flow, leading to a new growth of vessels and dilatation of walls. They are generally local, but may be quite extensive and variable in size. McCallum found forty small tumors in his case, while others describe either a small nodular tumor as in this case or as an extensive vascular tumor extending over several inches of the small bowel.

They may occur in the submucosa or under the serosa and may be simple or cavernous. This mass may consist of anastomosing net work of dilated veins or consist of varying sized cavernous spaces, lined by flattened endothelial cells. La Boulbene, and Judd and Rankin found, as in the present instance, the tumor in the duodenum. However, hemangiomata may be found in any part of the gastro-intestinal tract.

Case 2.—A woman, aged 33, married, presented herself for examination on Sept. 14, 1923, with a previous history of pulmonary tuberculosis: cough, night sweats, loss in weight, expectoration etc., and requiring a fourteen weeks' stay at a sanitarium.

One year before admission to the Michael Reese Hospital, she suffered from an acute attack of severe epigastric pain,

with nausea, vomiting and diarrhea. This pain was not relieved by food, but was when the patient lay down. She continued to have abdominal distress from time to time until two months ago, when following the eating of a considerable amount of fruit, she vomited everything she ate, and developed a diarrhea which continued for about a week. Her appetite was poor and she developed a recurrent diffuse abdominal pain immediately after eating. This pain lasted ten or fifteen minutes and was relieved by lying down. She would occasionally have nocturnal cramping pains in the upper abdomen, waking her up from her sleep. She vomited from time to time and on one occasion saw blood in the vomitus.

She entered the hospital (Michael Reese) on Sept. 10, 1923. Her symptoms continued as above described. Her cough persisted. A yellowish expectoration was negative for tubercle bacillus. The temperature ranged from 98.6 to 100.6 F. She lost 31 pounds in one year.

Data relative to her previous and family and menstrual history are negative as to their bearing on her present condition.

The points of interest in the examination are a poor state of nutrition, defective teeth, enlarged tonsils with large crypts, diminished resonance over both apices, exaggerated whispered sounds over the right apex, acute tenderness over the region of the cecum, the sensation of an indefinite mass in the epigastrium, and an enlarged retroverted and adherent uterine fundus.

Urine examination was negative. Blood: Hemoglobin, 78 per cent.; white blood corpuscles, 9,500; polymorphonuclears, 7 per cent.; small lymphocytes, 73 per cent.; large lymphocytes, 16 per cent.; polymorphonuclear eosinophils, 2 per cent.; transitionals, 1 per cent.; basophils, 1 per cent. Motor meal showed an empty aspiration at the end of seven hours. An Ewald at the end of one hour yielded too little to titrate and showed no free acid. Stool examination: No blood. Temperature, 99.4; pulse, 120; blood pressure, 105/80. Weight, 127½ pounds. Fluoroscopic examination showed no gross pathology in the lung. There was a very slight gastric residue in the stomach at the end of six hours. The stomach reached the level of the iliac crest and seemed to be regular in outline but emptied very rapidly. If a defect existed in the stomach, it was overlooked at the time of examination.

A diagnosis of tuberculosis peritonitis was made because of the history of pulmonary tuberculosis and a continuation There was a marked duodenal stasis.

of the symptoms at a later time, especially the cough, expectoration, loss in weight and continued temperature elevation, and the presence of an ill-defined epigastric mass considered to be a thickened mesentery or omentum. The tenderness in the right iliac region, which was very acute, was ascribed to an involvement of the cecum and appendix.

An exploratory operation revealed a normal appendix and cecum, and a large flat tumor involving the posterior and inferior walls of the stomach, almost but not invading the pylorus. There were no evidences of ulceration. This accounted for the absence of blood in the stools. The patient seemed to rally from the operation for a few hours, but died on the next day.

The following is the pathologist's description of the tumor removed at the operation and of the stomach at postmortem examination:

Section through the stomach removed at necropsy shows that the mucosa and submucosa are rather heavily infiltrated with small and large lymphocytes. There is on the serosa a fibrinous exudate which contains no inflammatory cells. There is in the lower layers of the mucosa of the small intestine a diffuse infiltration of large oval-shaped cells which are filled with granules of green pigment. The stomach removed at operation appeared as a gross specimen. The specimen includes the distal 9 cm. of the stomach from the pyloric sphincter.

The posterior wall is diffusely infiltrated with a very soft tissue which has a maximum thickness of 2.5 cm. There is a definite ulceration of the mucosa. The tumor involvement approaches the line of incision within 3 mm. There are several glands which seem to contain tumor tissue.

On microscopic examination, sections taken through the tumor and adjacent wall reveal very diffuse, invasive, malignant, neoplastic growth, the cells of which are of the small and round cell variety. The nuclei are vesiculated and contain many mitotic figures. There is a diffuse invasion of the underlying structures separating the gastric muscularis into distant layers. The growth also infiltrates the serosa and many of the lymphatics and some of the blood vessels contain tumor cells. The muscularis along the line of incision is infiltrated practically up to the distal extremities. Sections taken through the lymph glands reveal a partial replacement of the lymphoid structures with malignant cells which resemble the primary growth in the stomach in all respects.

In a recent article Sterling Ruffin[3] reviews the literature and mentions some of the cases he collected in the literature. The total number in the literature is not known, but from the infrequency of reports cannot be big. Twelve are from the Mayo Clinic. These have been reported in the *Journal of Laboratory and Clinical Medicine* of February, 1921. These cases were diagnosed lymphosarcoma. The only difference between lymphosarcoma and lymphoblastoma rests in the presence of small round cells (lymphocytes) in the former, and the larger, more rich in cytoplasm cell, the lymphoblast in the latter.

The tumor is very malignant, and is associated with glandular metastasis. Characteristic of the tumor is its tendency to extend by infiltration into the surrounding tissues, and regional lymphatics. All the layers of the stomach are indiscriminately invaded. The muscles fibers are invaded or pushed aside. There is a very little supportive tissue. The mass of the tumor consists of proliferating lymphoblastic tissue closely packed, showing numerous mitosis. The omentum, mesentery, intestine and other viscera can be invaded.

March 10, 1924.

A PRIMARY HYPERNEPHROMA OF THE LIVER

J. LISLE WILLIAMS

From the Pathological Laboratory of the Evanston Hospital, Evanston, Ill.

The patient, a woman, aged 68, entered the Evanston Hospital March 23, 1923, on the service of Dr. John McClellan, with symptoms of neuritis in the right shoulder and right side of the chest, a feeling of fulness and pressure in the epigastrium and about the heart, and difficulty in breathing. Two years previous to entrance she had an attack of abdominal pain and indigestion resulting from indiscretion in diet. At that time a mass was discovered in the right side of the

3. Ruffin, Sterling: Am. J. M. Sc. **165**: 1 (July) 1923. The most detailed report in the literature on Hemangioma is by Rodelius, E.: Virchows Arch. f. path. Anat. **246**: 426.

abdomen, apparently in the region of the kidney. This was not tender and caused no distress.

Physical examination on admission demonstrated generalized emaciation, rigidity of the right rectus muscle, an enlarged palpable liver, and a firm nodular mass below and behind the liver. This appeared to be about the same size as on a previous examination two years before.

An exploratory operation was performed by Dr. Carl B. Davis, and the liver was found to be studded with numerous tumor nodules, one of which was removed. Microscopic examination disclosed a hypernephroma. The patient recovered quickly from the operation, lived for seven months and died only after marked cachexia and weakness had developed.

Cross-section of the liver containing many nodules of hypernephroma tissue.

The necropsy performed one hour and a half after death revealed the following:

A primary hypernephroma of the liver with extension and metastases in the remainder of the organ; marked generalized emaciation and anemia; huge right hydrothorax; compression-atelectasis of the right lung; brown atrophy of the myocardium; chronic fibrous myocarditis, and hypostatic hyperemia and edema of the right lung.

The tumor tissue was found limited entirely to the liver and there were no metastases seen outside this organ. The liver together with the various tumor masses weighs 2,782 gm. The back surface of the tumor nodules is fairly well

encapsulated, their capsules apparently continuous with that of the liver. The tumor mass itself appears to have originated in the lower surface of the right lobe or within the substance of the same lobe and adjacent to the capsule. There are small masses of yellow fatty tissue like adrenal cortex adherent to the capsule. The largest nodule in this region is about 4 cm. in diameter, and near it, and almost continuous with this larger mass, are multiple smaller nodules 0.2 to 2.5 cm. in diameter. The substance of these masses is yellow, but some are necrotic and pale, whereas others are dark red from hemorrhage. Almost all the smaller nodules are separated from one another by small streaks and strands of liver tissue. Everywhere throughout the substance of the liver these same yellow nodules are present, the largest apparently about the middle of the upper half of the right lobe of the liver, 7 cm. in diameter; its upper pole is about 2 cm. from the diaphragmatic surface of the liver. The tumor tissue is densest near the lower border of the right lobe, which is apparently the site of the original tumor. It is estimated that at least four-fifths of the volume of the liver consists of tumor substance.

Both kidneys and adrenal glands are entirely separate from the liver although the right adrenal gland is greatly flattened and compressed from pressure by the liver.

Sections of the tumor tissue examined microscopically disclose the following:

The tumor nodules of the liver contain large cells with a clear vacuolated cytoplasm, arranged in solid masses and strands, extending out from a connective tissue stroma, and having the histological structure of a hypernephroma. There are numerous necrotic areas in these tumor nodules and many areas of hemorrhage. The substance of the liver is atrophic or necrotic; it contains areas of hemorrhage adjacent to the tumor masses and there is fibrous tissue in places, at the border of the tumor nodules. Some of the nodules in the liver are entirely necrotic.

It is quite probable that this tumor arose from aberrant adrenal cortex located within the capsule of the lower surface of the liver. The presence of adrenal tissue in the tissues adherent to the capsule of the liver makes this probability more likely. This location is one of the sites where adrenal rests are likely to occur.

March 10, 1924.

A DISSECTING ANEURYSM OF THE ARCH OF THE AORTA INNOMINATE AND COMMON CAROTID ARTERIES WITH RUPTURE INTO THE PERICARDIAL SAC

J. LISLE WILLIAMS

From the Pathological Laboratory of the Evanston Hospital, Evanston, Ill.

M. G., a man, aged 37, and a patient of Dr. George Dick, was admitted to the Evanston Hospital, March 16, 1923, in a peculiar semicomatose state with a history of an attack of agonizing pain in the precordium which followed the lifting of a small can of gasoline. The respirations were shallow and rapid, the pupils widely dilated and there was no radial pulse. The light reflex was present in the pupils. The deep reflexes were also present but sluggish. There was marked cyanosis of the face, ears and extremities. The heart tones were faint, the rhythm was regular, the rate 120. The outline of the cardiac dulness was normal. The patient's mental condition was very unusual for a coma in that he resisted any manipulations, such as attempts to open his eyelids or mouth, both of which were held tightly closed. At times he apparently understood what was said to him but did not respond. The systolic blood pressure was 60 mm. of mercury, the diastolic 0. Cardiac stimulants and hypodermoclysis improved the quality of the pulse and revived the patient slightly. While receiving his morning bath, the patient became angry with the nurse, attempted to rise and collapsed. He died within a few minutes, after having been in the hospital forty-five hours.

The postmortem examination made two hours after death demonstrated a fresh dissecting aneurysm of the arch of the aorta with extension into the innominate, the common carotid arteries and with spontaneous rupture into the pericardial sac and into the lumen of the left common carotid artery; huge hemopericardium; slight sclerosis of the lining of the aorta; necrosis of the occipital and posterior portion of the parietal lobes of the cerebrum and of the posterior portion of the left cerebellar hemisphere; recent infarcts of the left kidney; chronic fibrous myocarditis; anemia and cloudy swelling of the kidneys and myocardium; and passive hyperemia of the liver and spleen.

A more detailed account follows:

The pericardial sac is greatly distended and contains 860 gm. of dark red recently clotted and fluid blood. The heart is contracted, its chambers compressed. The pericardial sac extends far up about the great vessels at the base of the haert. In the back part of the wall of the aortic arch beginning about 2 cm. above the aortic ring there is a narow clean-cut slit in the outer layers, 2 cm. long, which communicates with the sac of the dissecting aneurysm and with that of the pericardium. The lining of the aorta is smooth, the wall thin, and there is very little subintimal fatty change.

There is slight aneurysmal dilatation of the ascending arch of the aorta. A fresh transverse slit 8 cm. long extends around the circumference of the aorta 3 cm. above the aorta ring. This rent extends through the intima and media, thus leaving the adventitia as the outer wall, the intima and media as the inner wall of the dissecting aneurysm. Only 1.5 cm. of the circumference of the intima remains unbroken. The dissection has spread toward the heart as far as the aortic ring and to a lesser degree within the loose tissue about the coronary sinus and in the fat along the course of the right coronary artery for 2 cm. From the heart the aneurysm extends upward around the arch to the innominate, left common carotid and left subclavian artery; thence upward on the right in front of the innominate and right common carotid artery to a point about 2 cm. below the bifurcation; on the left to a level 9 cm. below the bifurcation where the sac has ruptured back into the lumen of the common carotid artery with a slit 0.8 cm. long. As the dissection proceeds upward from the aorta, the outer wall gets thicker, the inner wall thinner so that in the left common carotid artery only the intima remains as the inner wall of the sac. Along the course of the posterior half of the left subclavian artery the aneurysm extends only 1 cm. The right subclavian artery however is not involved in the sac.

Sections of the aorta stained for spirochaetes by Levaditi's method disclosed no such organisms. Sections of the aortic wall stained with hemotoxylin and eosin reveal separation of some portions by clotted blood with small areas of lymphocytic and leucocytic invasion of the muscle layers of the media. In some portions the muscle fibers are necrotic. This sclerosis does not resemble that produced by syphilis.

The Wassermann reaction on the heart's blood was clearly negative.

It would appear that from the clinical course of events, that when the patient lifted a small can of gasoline his aorta

ruptured with the formation of a dissecting aneurysm. As this progresed up the carotid arteries it caused a cerebral anemia with the resulting mental symptoms. Then as he attempted to rise after becoming angry with the nurse the aneurysm broke into the pericardial sac producing a so-called heart "tamponade" and death.

March 10, 1924.

AN ENDOTHELIOMA OF THE POSTERIOR LOBE OF THE HYPOPHYSIS

J. LISLE WILLIAMS

From the Pathological Laboratory of the Evanston Hospital, Evanston, Ill.

M. E., a woman, aged 59, and a patient of Dr. George Dick, entered the Evanston Hospital Feb. 23, 1923, in coma with a history of having had a paralytic stroke a few hours before admission.

Physical examination revealed edema of the face, back of the trunk and lower extremities. Cheyne Stokes' breathing was marked, the pulse rapid, the heart greatly enlarged to the left. There was a urinous odor of the breath. The systolic blood pressure was 225 mm. of mercury, the diastolic 100 mm. The pupils did not react to light and inquiries made of the patient's relatives disclosed no previous history of visual disturbance. Venesection lowered the blood pressure, but failed to restore consciousness, and after twenty-six hours in the hospital the patient died.

Chemical examination of the blood two hours after entrance disclosed a blood urea nitrogen of 54 mg., a total nonprotein nitrogen of 88.2 mg., a uric acid of 8.7 mg., a creatinin of 3.4 mg. per 100 c.c., and an amino acid nitrogen of 12.3 mg. per 100 c.c.

Among the chief anatomical changes noted at the postmortem examination were spontaneous intracerebellar hemorrhage; chronic diffuse nephritis, secondary contracted kidneys; and edema of the brain and leptomeninges; marked hypertrophy and dilatation of the heart; marked senile sclerosis of the large arteries at the base of the brain and of the vertebral and common carotid arteries; huge subcutaneous lipoma of the left shoulder; multiple pigmented nevi of the skin of the trunk, face and extremities; subcutaneous fibroma of the left leg; cystadenoma of the thyroid

gland; multiple intramural fibromyomas of the uterus, and an endothelioma of the posterior lobe of the hypophysis.

This tumor lies above the hypophysis and the sella turcica and between the olfactory lobes of the brain. The surface is smooth, nodular and gray-pink. The tumor is about the size of a hulled walnut and fits into a depression on the under surface of the frontal lobes 3.5 x 2.5 x 2 cm., which is lined with unbroken leptomeninges. On the upper surface of this tumor there is a small amount of yellow lipoid-like material, some of which extends into the deeper portions. On the left side there is a small hornlike projection 2 cm. long. At no place has the tumor mass grown into the brain substance. The infundibulum extends over the lower and posterior surface of the tumor, which is firmly attached to the hypophysis and fills the upper part of the hypophyseal fossa. The substance of this tumor is soft and gray-pink.

Sections of this tumor (as shown under the microscope) reveal groups and masses of large slightly flattened deeply staining cells, irregularly arranged in interlacing lobules and masses. The stroma contains numerous engorged blood vessels. Sections through the posterior lobe demonstrate that the tumor is attached to this structure and apparently arises from it. The posterior lobe is partially destroyed. The anterior lobe is present and is unchanged.

Other sections stained for neuroglia fibers by phosphotungstic acid hemotoxylin disclose no such structures.

The patient's clinical history was that of achronic interstitial nephritis, and so far as could be learned there were no symptoms attributable to the tumor.

March 10, 1924.

PUTRID BRONCHIECTASIS

I. PILOT

From the Department of Pathology and Bacteriology of the University of Illinois College of Medicine, Chicago

In a study of putrid infections of the lungs a considerable number was found in patients with bronchiectasis. The results of the study of these patients can be summarized as follows:

1. Bronchiectasis is frequently complicated by putrid bronchitis, abscess and gangrene.

2. Clinically the complications are characterized by profuse expectoration of foul sputum, rise in tempera-

ture, leukocytosis and physical signs of pulmonary involvement. Metastatic putrid brain abscess may occur.

3. Bacteriological examinations of the sputum and of the lungs at necropsy reveal a fairly constant flora in which the fusiform bacillus, spirochetes and streptococci are usually found in symbiosis. In their morphological and cultural characteristics these organisms reveal those found about normal and diseased teeth and tonsils. In the metastatic cerebral abscesses the fusiform bacilli and cocci but no spirochetes were demonstrated.

4. The bacteriological findings suggested the use of neosalvarsan in patients with bronchiectasis with putrid infection. The response to therapy often was prompt with diminution of the expectoration and disappearance of the foul odor. The results, however, were not always permanent, for the bronchiectatic cavities remained and recurrence of symptoms occurred in some patients.

April 14, 1924.

THE DETERMINATION OF BRONCHOSPASM IN THE GUINEA-PIG AND ON CERTAIN RESULTS OBTAINED WITH THE METHOD

KARL K. KOESSLER
AND
JULIAN H. LEWIS

ABSTRACT

The method makes use of a device of Dennis E. Jackson employed by him in the dog for recording changes in intrathoracic pressure.

The procedure is briefly the following:

Into the wall of a stout hollow needle about 3½ inches long and one-sixteenth of an inch in diameter (Gauge 13), several small openings are made laterally; these holes cover a space about five-eighths of 1 inch

long. The pointed end is then closed air tight by soldering without changing the shape of this sharp end.

A guinea-pig not less than 300 gm. and preferably about 500 gm. in weight is tied back downward to a board, and under slight ether anesthesia the needle is passed directly through the chest walls just above the diaphragm at the time when the lungs are deflated.

A small tip of the skin picked up with a forceps is first removed with scissors and the needle is pushed at about the level of the fifth or sixth intercostal space through the muscular wall and parietal pleura of one side. Feeling one's way carefully with the point of the trocar, the lungs, liver, diaphragm and heart are carefully avoided and the needle point is thrust through the pleura and muscular wall of the other side; the skin bulging over it is best cut with a pair of scissors. The open end of the needle during this procedure is attached to a soft rubber tubing of small caliber which now is connected with a Marey tambour to see by the movement of the lever if the needle is corretly placed in the thoracic cavity. The pleural space, needle lumen, rubber tubing and tambour form a closed system, and any increase or decrease in pressure in the first produced by changes in lung volume and intrathoracic pressure is promptly transmitted to the sensitive diaphragm of the tambour and the *writing levers.*

The construction of *the latter* was an important item in working with as small an animal as the guinea-pig; to enable us to make the changes in intrapleural pressure as distinctive as possible we aimed to obtain a tracing with excursions of about 2 or 3 inches in amplitude. This was accomplished by using a double-jointed lever which transmits the relatively small excursions of the diaphragm of the tambour with considerable magnification to the drum. Inspiration is thus indicated by the downward stroke of the writing point of the lever, expiration by its upward movement. To be able to ascribe the pressure changes in the intrathoracic space to changes in lung volume as caused by contraction of the bronchioles, it is necessary to remove active respiration by cutting off all connections of the respiratory centers with the periphery through pithing of the ani-

mal. Under deep ether anesthesia a small median incision of the skin over the occiput exposes the skull and by means of a stiff brass wire passed through an opening made with a sharply pointed probe the brain and the spinal cord are destroyed thoroughly. Instantly, when this has been done a tracheal cannula is tied into the larynx and passive artificial respiration with positive pressure is instituted at once. For this purpose compressed air from a tank is sent intermittently by means of an interrupting valve, regulated by a small motor (one-tenth horsepower) into the tracheal cannula. To regulate the amount and pressure of air admitted to the lungs, a side tube is attached to the half-inch metal pipe which carries the air from the tank to the tracheal cannula. This side tubing is of the same caliber, one-half inch, and by means of a piece of rubber tubing and a second clamp excessive pressure and quantities of air are avoided and an optimum volume of air producing the desired size of the excursions of the lever is rhythmically introduced into the lungs. The rate of inflations should best be about twenty per minute. Just above the tracheal cannula a — tubing of glass of about 4 mm. inside diameter is inserted to permit facile egress of the air from the lungs during passive expiration.

If the pithing has been done correctly and artificial respiration has been instituted promptly, the heart action continues unimpaired and may remain so for hours.

The external jugular vein is then exposed and a small glass cannula is tied into it. The glass cannula has been previously connected by means of a soft rubber tubing to a glass burette and the burette, tubing and cannula are filled with physiological salt solution. The solutions to be tested for their bronchospastic action are injected by means of a syringe and a fine needle into the lumen of the rubber tubing, and thus reach the right heart and pulmonary circulation directly.

The application of the method (*a*) to the study of the pharmacodynamic action of bacterial poisons, and (*b*) to the analysis of experimental anaphylaxis, is discussed. Its routine use in all studies on anaphylaxis in the guinea-pig is advocated.

April 14, 1924.

PSEUDOLEUKEMIA GASTRO-INTESTINALIS

ALFRED D. BIGGS*

AND

ARTHUR R. ELLIOTT

From the Pathological Laboratory of St. Luke's Hospital, Chicago

Cohnheim, in 1865, described as pseudoleukemia tissue changes like those occurring with leukemia but without the usual increase in the number of leukocytes of the blood. Since the original description there have been recorded as pseudoleukemia a number of diseases, such as Hodgkin's disease, lymphosarcoma, Von Jaksch's disease, multiple myeloma, Gaucher's disease, Banti's disease and even the lymph gland hyperplasia of tuberculosis and syphilis. Sternberg, in 1912, reviewed the literature and emphasized the distintive features of pseudoleukemia and the diseases with which it has been confused. He regards pseudoleukemia as a distinct and definite disease as originally described by Cohnheim.

A review of the literature by Wells and Maver in 1904 summarizes 237 reports of true pseudoleukemia. In seven of these the changes were confined largely to the gastro-intestinal tract and consisted of a hyperplasia of the lymphoid tissue. They reported another and suggested the term pseudoleukemia gastro-intestinalis for this small but distinct group. Reviews of the literature by Symmers in 1909 and 1918 mention four additional reports. These do not include a report by Warfield and Kristjanson made in 1916 in which a postmorten examination is recorded with tissue changes like those described by Wells and Maver, alterations that the authors prefer to designate as abdominal Hodgkin's. There seems to be no report of the disease since 1918. If Warfield and Kristjanson's report be included with those already mentioned and the one to be mentioned here, there are on record now fourteen reports of gastro-intestinal pseudoleukemia.

* The John Jay Borland Fellow in Medicine, 1923-1924.

The first record of this disease seems to be that by Briquet in 1838 almost thirty years before Cohnheim made his description. Briquet described it as a very remarkable disorder of the stomach, large and small bowel, in which the mucosa is thrown into folds like cerebral convolutions by an overgrowth of the lymph follicles. He emphasized the essential characteristic, namely, that the tissues other than the mucous membrane are not affected.

Some hyperplasia of the spleen or lymph gland enlargement usually accompanies the disease. In the fourteen reports of gastro-intestinal pseudoleukemia, splenic enlargement is mentioned with ten, and enlargement of the abdominal lymph glands with twelve.

Generally, pseudoleukemia is described as a simple hyperplasia of the lymphoid tissue.

The patient, aged 25, an Argentenian, by occupation a civil engineer, had two severe hemorrhages of the stomach April 5 and 7, 1921, after which he came to St. Luke's Hospital in an ambulance and was admitted to the medical "A" service. He was exsanguinated, pulse, 100; temperature, 99 F.; hemoglobin, 50 per cent. There was moderate tenderness of the epigastrium. The patient remained in the hospital for one month on a bland diet and gradually improved. The clinical diagnosis at that time was gastric ulcer.

During the next eighteen months he was not under medical observation and had numerous exacerbations and remissions of his gastric symptoms. In November, 1922, an exploratory laparotomy was made in Kansas City, and the surgeon, believing that a carcinoma of the stomach existed, performed a gastro-enterostomy. After a slow recovery he came to the Presbyterian Hospital, Chicago, Dec. 28, 1922. He remained there on ulcer treatment for about four weeks. He came to St. Luke's Hospital a second time, Feb. 7, 1923. He then complained of loss of weight and strength, abdominal pain, vomiting and of having small quantities of blood in the stool and vomitus. Roentgen-ray examination of the stomach (Dr. E. L. Jenkinson) revealed an irregular outline of both curvatures. The clinical diagnosis at this time was carcinoma of the stomach. During the next six months the patient was ambulatory and at times confined to his bed. The leukocytes of the blood were between 6,000 and 8,000 at intervals between the time of entrance and death.

During the last two months of his life he rapidly became emaciated and weak. Ten quarts of a clear fluid were removed from his abdomen a month before death (Sept. 29, 1923).

The postmortem examination made by Drs. Edwin F. Hirsch and Allen C. Nickel demonstrated the following essential changes:

About 1,500 c.c. of a slightly cloudy fluid is contained in the abdominal cavity. The parietal and visceral peritoneum is thickened and scarred by fibrous tissue. The mesentery is shortened and hard with white fibrous-like tissue and 7 to 10 mm. thick. The great omentum is matted together along the transverse colon and contains an abundance of fibrous tissue. The lower portion of the cisterna chyli is surrounded by a mass of lymphoid tissue 3.5 cm. long and 0.8 cm. thick, but its lumen is not constricted.

The wall of the entire stomach is thickened and rigid especially that of the distal one third. Although empty, it resembles a stomach moderately distended with food, and the walls do not collapse when it is opened. The muscle coats and the peritoneum are 6 to 8 mm. thick. The mucosa is markedly thickened and thrown into large irregular ridges and polypoid masses, the largest of which is 2 x 5 cm. and elevated 4 cm. The wall of the entire small bowel is thickened and firm, similar to that of the stomach, but the changes are less marked. In the jejunum the changes are least marked and confined largely to the portion of the bowel next to the mesenteric attachment. Practically the entire circumference of the ileum throughout is involved so that its lumen stands out like a markedly sclerosed blood vessel. Where the nodules of the small bowel are discrete they average 2 to 4 mm. in diameter; the lymphoid hyperplasia is so marked that in most places it is impossible to tell where one group of the agminated follicles ends and another begins. The changes in the colon are similar to those of the ileum and are most marked in the ascending and transverse portions. There is nowhere any ulceration of the mucosa of the gastro-intestinal tract.

The lymph glands of the region of the cardia of the stomach are 2 cm. long and firm. Inside they are gray-red. Those of both the lesser curvature and the greater curvature have a consistency of cartilage, are up to 2 cm. long and inside are gray. Most of those of the greater curvature are imbedded in a mass of omental and fibrous tissue, 5 x 3 x 2 cm. located 5 cm. proximal to the pylorus.

There is no enlargement of the inguinal, axillary, cervical or thoracic lymph glands, except one subclavicular gland

of the left side 0.4 mm. long. This gland is gray-pink and soft. The spleen is small and weighs 55 gm. The malpighian corpuscles are indistinct. There are no nodules in the liver or kidneys.

There are two predominating types of cells in the sections of these tissues, one a small normal appearing lymphocyte, another three or four times larger and resembling closely a large lymphocyte. These cells are up to 12 microns in diameter and some have more than one nucleus. Otherwise there are no giant cells and the tissue changes do not resemble Hodgkin's disease. All coats of the stomach are greatly thickened by fibrous tissue and lymphoid cells. Many lymphocytes lie between the tubules and at their base. There are places where the cells lie between the muscle fibers and connective tissue fibers. There are other places where the muscular and peritoneal coats are replaced by a single layer of fibrous tissue in which many lymphocytes lie. The microscopic changes of the intestines resemble those of the stomach but to a lesser degree.

There is a marked increase in the connective tissue of the abdominal lymph glands. Their sinuses are wide and stand out distinctly and are filled with the larger type of lymphocytes. The lymph nodes are composed of the smaller more normal appearing lymphocytes. The peritoneum of the posterior abdominal wall is greatly thickened and studded with masses of these lymphocytes. There seems to be an infiltration of the walls of many of the abdominal blood vessels by these cells. They lie between the muscle and connective tissue fibers of the vessel walls. There is a distinct infiltration of these larger lymphocytic cells along the lymph channels of the lung. This resembles the Kundrat type of lymphosarcoma. Many of the lymph channels of the lungs are infiltrated similar to those of the abdomen. A few of these cells are scattered in the epicardium; none in the myocardium.

CONCLUSIONS

The tissue changes generally agree with those described in the other thirteen reports. But there seems to be an infiltration in the lymphaties of the lungs, and in the walls of many blood vessels. Otherwise the tissue changes reported here are a hyperplasia of the lymphoid tissue and are almost altogether confined to the gastro-intestinal tract.

A more complete report with bibliography will be published elsewhere.

April 14, 1924.

A STUDY OF STREPTOCOCCI FROM CHRONIC INFECTION OF THE CERVIX UTERI AND THE FALLOPIAN TUBES

C. W. BARRETT, A. F. LASH
AND
I. PILOT

From the Department of Gynecology and from the Department of Pathology and Bacteriology, University of Illinois College of Medicine, Chicago

This bacteriological study was made of fallopian tubes, grossly inflamed, from 100 patients, and of cervices from forty of the same patients. The media used was ascitic broth, ascitic agar, blood agar, and Endo plates. Streptococci were isolated in pure culture and differentiated by means of blood agar plates, fermentation and litmus milk reactions. The pathogenicity of the different strains was determined by rabbit inoculations.

The conclusions reached from the above study are:

1. Streptococci are frequent in chronic infections of the cervix (40 per cent.) and of the fallopian tubes (35 per cent.). *Streptococcus hemolyticus* occurred in 14 per cent. of the cultures of the fallopian tubes and 5 per cent. of the cultures from the cervix, while *Streptococcus viridans* occurred in 21 per cent. of the cultures of the fallopian tubes and 27.5 per cent. of the cultures from the cervix.

2. There appears to be no relation between the incidence of streptococci in the cervix and that in the fallopian tubes.

3. The morphological and cultural characteristics of the streptococci isolated from the diseased cervix and fallopian tubes resemble those isolated from abscesses, peritonitis, fatal streptococcus infections.

4. The pathogenicity of the different strains of streptococci as determined by rabbit inoculations is similar to the strains isolated from various streptococcus infec-

tions. No specificity for the fallopian tubes was demonstrated.

May 12, 1924.

THE HAZARD OF SURGICAL ANESTHESIA WITH SYPHILIS OF THE BRAIN *

E. R. LeCOUNT
AND
H. A. SINGER

From the Pathological Laboratories of the Cook County Hospital

SUMMARY

That syphilis may affect the healing of wounds has been known since the sixteenth century. Aside, however, from its local influence, syphilis offers to the surgeon an entirely different concern in respect to its general effects upon the patient. Sudden death in luetic subjects following relatively minor surgical procedures is usually explained on the basis of an "underminded constitution making the patient unable to withstand the sudden strain to which he is subjected." That death may be the result of an unsuspected or unrecognized syphilis of the brain is exemplified by the following two reports:

Case 1 concerns a colored female, aged 27, who complained of leukorrhea and backache and was found to have a retroverted uterus for which a round ligament shortening was advised. The patient suffered also for several years from severe headaches. There was a history of successive miscarriages. The anesthesia consisted of a preliminary narcotic (morphin sulphate gr. 1/6 and atropin sulphate gr. 1/150) and ether inhalations administered for a period of fifty minutes. About three and one-half hours after the conclusion of the operation, the patient developed signs of respiratory paralysis, shortly after which death occurred. At the postmortem examination (E. R. L.) there was found no noteworthy change outside of the brain. The microscopic diagnosis based on a careful study of the brain (Dr. C. B. Semerak) reads: "General syphilitic meningoencephalitis, peri-arteritis, and endarteritis; edema and anemia of the brain." These lantern slides reproduced from photomicro-

graphs taken from microscopic sections, illustrate the type of inflammation present in all portions of the brain examined.

Case 2 is that of a white male, aged 52, who entered the hospital on account of hemorrhoids. In addition to his rectal complaints, he stated he experienced paresthesias involving various portions of the body. The pupils were found to be slightly unequal and to respond sluggishly to light. The blood Wassermann was positive. A hypodermic of morphin and atropin was given prior to the operation. The administration of ether had been in progress only ten minutes (the operation having not yet been started), when the patient stopped breathing. In this body there was found (E.R.L.) a disseminated syphilitic fibrous leptomeningitis which furnished the only anatomical basis for death. The other changes of note were a marked leutic aortitis and stellate scars of the liver, presumably syphilitic in origin.

Although an extended search failed to lead to the discovery of case reports similar to the two related in this paper, it is not taken to mean that such observations have not been previously made or recorded. However, it does seem to justify the belief that the knowledge of the possible danger of anesthesia in cases of relatively asymptomatic or slightly active neurosyphilis is not widespread.

CONCLUSIONS

1. General anesthesia with syphilis of the brain may prove fatal.

2. With symptoms or signs suggestive of alterations of any sort in the central nervous system, a thorough examination to determine the presence of a syphilitic infection should precede any elective operation.

May 12, 1924.

CALCIFICATION OF THE MITRAL RING WITHOUT PREVIOUS INFECTION

B. M. GASUL

From the Pathological Institute of Rush Medical College, aided by a grant from the American Medical Association

I wish to call your attention to a form of an endocarditis which, so far as I am aware, has not been dis-

* The complete paper will be published in The Jour. A. M. A.

cussed in English medical literature, and which has received but little consideration in foreign literature, that is, calcification of the mitral ring, not the leaflets and apparently without previous infection.

That such lesions occur without previous acute endocarditis has been recognized. Adami, Osler, Austin Flint and others speak of chronic mitral endocarditis not due to previous acute endocarditis, and William Thalhimer [1] speaks of nonbacterial, nonrheumatic, chronic endocarditis which he thinks might be due to some general toxic or some distant inflammatory process which leads to a primary trauma of the heart valve leading to a chronic inflammation. The important point about acute lesions is that they occur at the free margin of the valves, close to the line of closure of the leaflets and usually on the auricular surface.

Dr. LeCount has observed a condition of calcification of the mitral ring with the lesion at the base of the mitral ring and on the ventricular surface where acute lesions are not met with, and Dr. VanDyke studied five hearts under Dr. LeCount's direction. Later I studied five additional hearts and reviewed the literature on this subject.

All our hearts possess an annulus fibrosis (normally a soft, fine ring, somewhat thicker in the region of the trigonum fibrosum) which is everywhere affected. It is hard, in some hearts, bony-like in consistency; in others involving only the ring, and in others lime deposits extend into the valves and deep in the adjacent musculature of the heart.

Microscopically, various changes are seen. In some only slight retrogressive changes are present, the nuclei partially disintegrated and the muscle fibers staining pink. In others, an obliterating endarteritis of the arterioles supplying the heart muscle adjacent to the mitral ring is present with complete necrosis of the fibers and variously sized circumscribed patches of calcification more or less blue with hematoxylin. I found no evidence of inflammation of the leaflets and an inflammatory cellular exudate is either slight or absent.

1. Thalhimer, William: Arch. Int. Med. **30**: 321, 1922.

Mention is made in the literature that the fibrous ring surrounding the mitral orifice may become firmer than normal and infiltrated with lime and the author, Sansom [2] dismisses the explanation of this by merely saying that these changes may be associated with otheromatous degenerations or may represent syphilitic gummas which have become calcified, and Flint [3] speaks of "mitral lesions consisting of thickening and contraction of the valvular curtains—and accumulation of masses of calcareous matter at the base of the curtains, diminishing the size of the auriculoventricular orifice and presenting an irregular surface to the current of blood"; but the author explains these conditions as results of inflammation.

Mention of this calcification is made more extensively in the German literature, and Koninger [4] speaks of cases of calcification of the mitral ring which are usually attributed to either chronic endocarditis or to arteriosclerosis, and saying that we do not know the cause of this transformation, but they are different from the changes observed in arteriosclerosis or following acute endocarditis.

Dr. W. E. Dewitzky [5] discusses these changes more fully and he believes that sclerosis of the fibrous rings is a rather common occurrence, and that there is hardly a heart which after the age of 25 does not show some change in the annulus fibrosus. According to this author, the sclerosis is a gradual physiological change, the fibers of the connective tissue gradually lose their slenderness, become denser and poorer in nuclei, leading finally to the formation of a distinct necrosis of the fibrous tissue and calcification.

August Steven [6] discusses the clinical and pathological changes in eighteen hearts which showed no calcification of the mitral ring, and concludes that these changes are

2. Sansom, A. E.: Allbutt's System of Medicine **6**: 341, 1909, London, Macmillan & Co.
3. Flint, Austin: Practical Treatise on Diagnosis, Pathology and Treatment of Diseases of the Heart, Philadelphia, 1859.
4. Koninger: Histologische Untersuchungen über Endokarditis, Leipzig, 1923, p. 312.
5. Dewitzky, W. E.: Virchows Arch. f. path. Anat. und Physiol. und. f. Klin. Med. **199**: 1910, Berlin.
6. Steven, August: Inaugural Dissertation, aus Wune in Westfalen, 1918.

due to a wearing down process in the annulus fibrosus due to the constant strain that this ring is subjected to during life.

There has been observed by many workers [7] that in cases of narrowing or stenosis of the isthmus of the aorta with the resulting high blood pressure proximal to the occlusion, the aortic leaflets quite commonly are altered with changes which have been generally called "chronic endocarditis." Dr. LeCount sees an analogy between the calcification of the mitral ring and the changes that may occur at the attached margins of the aortic leaflets in coarctation of the aorta. Just as the aortic leaflets may tear due to the resulting high blood pressure proximal to the occlusion, so may the mitral leaflets with a high blood pressure in the left ventricle which drives the mitral leaflets in the direction of the left auricle, tear at the attached margins on the ventricular side. This tearing, of course, results in hemorrhage, clot formation, interference with the blood supply and the degenerative changes mentioned above, and as in other dead tissue lime salts are subsequently deposited.

It seems to me that a combination of Dr. Dewitzky's and Dr. LeCount's explanation explains this calcification. There is no doubt that the mitral ring which is made up of connective tissue has not the contractile powers that the rest of the heart muscle has. This ring is constantly subjected to wear and tear and given a high blood pressure in the left ventricle, it may well tear at the attached margins and, of course, on the ventricular side. The blood pressure in the left ventricle does not have to be permanently high, and any sudden increase in the pressure, as following some unusual exertion, running after a street car, a fight, or the performance of some athletic test, may be sufficient to produce minute tears and the subsequent changes described.

May 12, 1924.

7. LeCount, E. R.: Occlusion of the Aortic Arch at the Isthmus, in Trans. Chicago Path. Soc., Nov. 10, 1913. Albott, M. E.: Coarctation of the Aorta, Osler's System of Modern Medicine **4**: 121, 1915. Strauer: Deutsch. Arch. f. klin. Med. **95**: 344, 1909. Monckeberg: Verhandl. d. d. peth. Gesellsch. **12**: 242, 1908.

TRANSACTIONS OF THE
CHICAGO PATHOLOGICAL SOCIETY

Vol. XII June 1, 1925 No. III

POLITICAL ACTIVITY OF VIRCHOW

PRESIDENTIAL ADDRESS

WILLIAM F. PETERSEN

If at this time I take the liberty, for such it is, to brush off a bit of the accumulated dust from one of the patron saints of our guild, a number of motives underlie my selection of the topic. With Virchow the pathologist we are conversant. So with Virchow the anthropologist and Virchow the comparative anatomist. But with the fiery, impetuous idealist—with the friend of the humble, the builder of hospitals, the advocate of universal education, the party organizer and the chairman of the budget committee of the Berlin city council and the Reichstag, with the lifelong opponent of Bismarck—with that man most of us are unfamiliar. Perhaps because Americans came into contact with him only in his later years. Perhaps because they came only to see the pathologist and never sensed the many hidden currents of activity which made Virchow truly the great citizen of his country.

These less known activities made him so intensely human, and withal are so characteristic of what we might expect of a great medical scientist that I believe it may be refreshing to recall them, the more so since the increasing political tension which has followed the war may give us greater insight and sympathy for the reaction that we witness in the young Virchow.

Born of parents in very modest circumstances in a small Pommeranian town, where social lines of demarcation were sharply drawn between the wealthy landowners and the poorer townspeople and farm laborers; with still recent memories of the Napoleonic era,

French occupation, hunger and misery, Virchow's boyhood impressions were bound to be rather somber. His father, an intelligent but unsuccessful man, was a paradoxical character, most conservative in his political and social views, but an outspoken skeptic in his religious concepts.

Following his gymnasial training, Virchow's university years were years of great political unrest. The wars had been followed by thorough-going reaction made more evident then, perhaps, because the symbols of political power were simpler and more direct than now. Europe accepted absolutism as a relief from the disorganization of war, but the evils of the system finally led to revolt, revolt to further oppression and so on in an unending vicious circle.

Virchow came to Berlin in 1839, and the following ten years witnessed the entire revolution of such a cycle. Virchow lived and was an integral part of every phase of the liberal movement, for, as he once wrote his father, "A scientist can only be a republican."

But he became a republican gradually. His letters to his father from the early Berlin days begin to be tinged with decidedly liberal views, veiled a bit, perhaps, because the father was a conservative, but quite apparent when we read between the lines. So, in a letter dated December, 1840, he encloses a parody on a Prussian statesman and adds, "The text is blunt but true. His Majesty, when he first heard the song, is said to have remarked that it marked the first sad day of his reign. A spirit of freedom and unfathomed effort seems to make itself felt in the nation; the times seem pregnant with profound unrest, the seeds of masterful strength lie dormant in the womb of time." Nor must we assume that such early views were merely the passing phase that so many half-baked university students go through. Virchow was too mature even as a student for that. One has but to survey his Reifeprufung (examination of maturity) of the gymnasium to realize that. "Das Leben ist ein ernstes Geschäft" fitly epitomizes his entire outlook on life.

Virchow was a student in the Army Medical School. One uncle was a major in the army, another an archi-

tect of note in the Royal Bureau of Architecture, but that did not for a moment deter his liberal bent. In the years before his graduation (1843-44) his letters contain an occasional reference similar to that which I have quoted. "The senseless religious strife, the daily sharpening of political differences, the social evils of the day become more and more menacing; society is becoming cognizant of the approaching danger and the daily victims of the government only aggravate the situation."

But in the meantime his life was filled by an ever increasing routine of subaltern duties and study and research. Undeniably brilliant and conscientious, he became the pride of the older army medical men connected with the school, and because of this his liberal views were readily overlooked. In 1843 he received his doctor's degree, was appointed to the Charité and shortly after became the assistant of Froriep in the pathologic anatomy. It was during this period that his dissertation on rheumatic iritis and his paper on phlebitis were delivered. With them began a period of tremendous scientific activity and of other activities as well.

The astonishing and really marvelous feature of Virchow's whole career is, to my mind, the fact that at 25 he was already a master, recognized as such by his colleagues, possessing all the mental equipment and force of character that distinguished him and stamped his name indelibly on modern medicine. Mature, sure and conscious of his power, he suddenly appears in public view. There is nothing hesitant, nothing amateurish, nothing self-conscious, and he accepts his rôle of superiority as his due.

Curiously enough, this latter feature in the young man seems to have caused little comment. We might suppose him an unbearable prig, lecturing his seniors, belittling their labors and caustically commenting on the medical and political failings of the day. Certainly an opinionated young man at the very least! If there was this reaction to him I fail to find it recorded in the contemporary biographies. Nor had he much sense

of humor to soften his severe young outlook. Sarcasm a plenty, but little humor.

The year 1847 witnessed the beginning of revolt in Europe, first in Schleswig-Holstein against the Danes. In Berlin the provincial assizes were convened for the first time to authorize a loan for the autocratic government, and with beginning financial depression occasional riots took place in the city. The king was stubbornly opposed to political reform or concession of any kind.

Virchow's letters to his father contain little of any except political news during this period, his whole lively interest seems to have centered on the burning questions of the day. Small wonder, with revolution and unrest in France, Italy, Hungary and Switzerland. But he does add in one of his letters, "I am doing much experimenting on dogs and we are preparing the second number of the Archives" (Virchow contributed eight of the first fourteen papers of these two numbers).

Then came starvation and typhus in Silesia. Together with Barez, Virchow, still de facto an army surgeon, was detailed to investigate the conditions. Here for the first time he came into actual contact with the results of misgovernment; with starvation, misery, poverty, filth, disease, ignorance and servility. He was aghast. He blamed the church and he blamed the state. And with the completion of his task his liberal views had crystallized so that he returned to Berlin a thorough-going radical, keen for the revolution—in government, in medicine, in the social and the economic structure. May I read a few excerpts from the report of this young army surgeon to his government?

"Medicine will do little," he states. "The injury is much deeper than can be cured by mere drug mixtures. Social reforms are needed and only social reforms will cure the evils from which the population of Silesia suffers. Real democracy and with it education and freedom and prosperity."

"Moreover," continues Virchow, "large parts of Silesia are Slavic in culture, language and aspiration. Why not, in a national reorganization, turn Silesia over to the great Slavic neighbor?"

"The working hour of the laborer should only be long enough to wrest from the soil sufficient sustenance for the comfortable existence of the race; never should he be forced to waste his best effort in the accumulation of capital. Capital is merely an assignment for indulgence or enjoyment, not by any means its real attainment. That seldom bears any ratio to the capital involved."

Rather strong medicine for government bureaucrats to swallow and, needless to say, it did not tend to make this particular army surgeon popular with the all-highest. But in the meantime political events had reached a climax, and Virchow was fully prepared to accept the consequences of his ideal—"a complete and untrammeled democracy."

On the 11th of March he writes his father, "I reached Berlin last Friday. I had hurried (from Silesia) partly because of the unbearable weather, partly because of the political situation. You have probably followed the events. While I have expected them for some time, I myself had doubts that they would reach a climax just now. The position of the government is a hopeless one at present and it seems curious that the king must still endeavor to treat his people as though they were a mob of children. He postpones vital concessions, such as the freedom of the press, indefinitely. Feeling is at high tension. I do not know how soon the actual revolt will take place. The troops are constantly in motion." On the 19th of the month he describes the street battles. "Since yesterday we are in the midst of the fighting. For twelve hours we have had the roar of guns and today the people have gained the victory and royalty has hardly saved a few shreds of its power. Before I go into details, be assured that I personally am unharmed." He then describes the fighting, and of his own share writes: "My own participation in the uprising was relatively modest. I helped to build some of the barricades. I could only get an old pistol, itself of little use because the soldiers shot at long range. With the small number of citizens holding our barricade a hand combat was out of the question. Whether we can be of any further service I do not know. We

are to have meeting tomorrow at the residence of Dr. Meyer"—(one of Berlin's leading gynecologists and later the father-in-law of Virchow). "A general arming of all property holding citizens has already been determined upon as well as the organization of a militia."

In Schleich's memoirs he relates that his father, at that time a student in Berlin, frequently told how young Virchow, at the first word of the fighting, rushed into his room at the Charité, shouting the news and looking everywhere for a gun.

That the revolution finally failed you know; failed largely from the lack of leadership of the liberals. But in the interim Virchow had turned his attention to reform in other fields—in medicine, in medical teaching, in university administration, in hospital management. In a weekly that he established with Leubuscher you can find his views emphatically advanced.

He writes for instance: "It is not sufficient that the state should give opportunity of a bare existence, that the state should aid every individual who has been incapacitated, to create an existence for himself. The state should do much more. It should provide hygienic living conditions. This follows simply from the concept of the state as personification of the moral consciousness of the mass; from the joint responsibility of all for one. It is fundamentally wrong to substitute the Christian charity of a few individuals for the plain duty of society as a whole."

In the University Virchow agitated for the greater participation in the control of the organization for the members of the faculty who were not full professors. In the hospitals for increased facilities for the poor. Everywhere he was an advocate for the disinherited.

And so it came about that he came to be regarded as one of the principal intellectual leaders of the revolt, even if not one of the political leaders. His addresses were fiery enough, and he spoke often and well and his printed manifestoes were read widely by the people. In the councils of the clubs and political gatherings he was, however, calm and reasoning. Elected to the con-

stitutional convention by two constituencies, he was unable to take a seat because of his youthful age.

But the government did not relish these activities of the young prosector. Virchow's position in the profession was by this time sufficiently influential that when the reaction set in he was not greatly molested, particularly when he agreed to carry on no further agitation against the government. Nevertheless a change of scene seemed desirable and he was glad indeed to accept the Professorship at Würzburg. His fruitful scientific activity there, amid more peaceful surroundings, is known to you.

If we analyze Virchow's reaction to the political events of the day we find nothing incongruous. It harmonizes with the outlook of the scientist. Just as in his science he brooked no tradition and endeavored honesty to penetrate to the basis of observed phenomena, so he discarded all tradition in politics, uninfluenced by any feeling of reverence for old forms or personal bonds. The accepted political organization of the state in his day was the absolute monarchy, with its two inevitable appendages, the bureaucracy and the military. He who was endowed with the sharp vision of a Virchow could not but see the responsibility of this political system for the evils then existing in the state. Add to this the fact that Virchow was strengthened in his opinion by contact and precept of all the intellectuals of the time. Liberalism was rampant. Then, too, there came the added factor that Virchow came from the common, relatively disenfranchised class and that in advocating this cause he was but true to himself.

Consider his religious skepticism. His scientific training and orientation made natural that he should throw his whole weight against the philistines and the bigots in the church. Virchow, with the parental example before him, held the church largely responsible for the opposition to popular education and he stepped forward very early to the front ranks in this battle. Among scientists he was perhaps the first to organize and give popular lectures for working people.

Perhaps his intense interest in the revolution was after all the revelation of the real humanity of Virchow. Despite his seeming austerity and aloofness, more apparent in his later years, Virchow was a kindly individual and was swept away by the heroic quality of the mass movement for liberty.

He enjoyed the opportunity for organizing, a talent which he possessed to a marked degree. Finally the political revolution came at a time when he was part and parcel of the medical revolution and the mental attitude was quite in tune with his scientific work that had heretofore occupied so much of his time. How profoundly he entered into the spirit of the revolution becomes apparent when we find that the ideals which he then upheld remained as fixed guiding stars throughout his entire career.

Many years later in an address at the Reichstag, Virchow, tiring of the crass materialism everywhere apparent, reproached his hearers: "Gentlemen, as you are aware, the German people have turned to other, useful directions. We, who once carried the German ideals, live now in the rather uncomfortable state in which we cannot shed them. You, gentlemen, who never fought for those ideals, may well concern yourselves with grain and steel and spirits; it is probably a comfortable existence but one which we do not envy you. Follow such material interests as you will, you cannot deny to our small group the right to remind our nation of the old ideals. We cherished those ideals, indeed we raised the idea of German unity to maturity at a time when the Chancellor knew nothing of them, indeed, opposed them."

In 1858, Virchow returned to Berlin. Johannes Müller, who had much to do with bringing him back, may have thought that the quiet of Würzburg had caused Virchow to forget his political activity and his ideals. Not so. His most useful era as a public spirited citizen then really begins. The very next year he was elected to the Board of Aldermen and served continuously for thirty-four years. When he was first elected it was a very small body, all capable men, progressive and imbued with a spirit of public service.

Virchow's accession strengthened the group materially and, paradoxical as it may seem, it was in the field of finance that his chief activity developed. Here his ability to organize, to draw rapid but accurate conclusions from even a transient survey of the field, led to a striking improvement. He joined no particular party, but gathered about him a group of men through whose efforts the marvelous growth of Berlin was systematically directed into certain well ordered channels with much less confusion and reduplication of effort than usually attends such phenomena. Berlin, under this liberal government, owed much to the active participation of Virchow in its development into one of the healthiest and cleanest of continental cities. He practically planned the method of sewage disposal, he was an active member of the committees which planned, built and organized the municipal hospitals at Friedrichshein, Moabit, Dalldorf and the Kaiser Friedrich Hospital for Children.

As one of the founders of the Progressive party (Fortschritts Partei), Virchow began to take an active part in national politics and was elected for two constituencies for the Reichstag, accepting at first that from Saarbrucken. In the Reichstag he promptly grasped the advantage that the power of the budget gave the electorate and devoted the greater part of his time to budgetary affairs. "We will," he said in one of his first speeches, "use the right of control given us by the constitution and we shall use it for the purposes and in the way that the constitution has in view." Another of his first addresses concerned the violation of certain rights of the smaller constituent states of the federated empire. As usual he was defending the under dog.

Both in debate and in committee work his energy seemed boundless. Even in his parliamentary work he was never superficial. He wanted facts; he never tired till he got them, no matter what the difficulty. Naturally, his most interesting passages at arms were with Bismarck, with whom he never could agree.

Such political activity, which to the normal individual might seem more than sufficient to fill a life time, was merely a relaxation for Virchow. He enjoyed the

debates. With his keen memory, his intellectual capacity and his biting sarcasm, he was more than a match for his opponents. As we might expect, he was forever advocating measures of social reform that even to our enlightened age may seem purely idealistic.

In 1860, long before the social democratic party came into prominence, he demanded a reduction of working hours to a minimum in the interests of general cultural development, the education, and the home life of the toiler. And as for disarmament, we find Virchow offering a resolution in 1869 in the Prussian Diet in which he declared that the growing and continued armaments of the continental powers were not due to the national jealousies of the peoples but to the intrigues of the cabinets, and he accordingly insisted that all military expenses be curtailed and that the total disarmament of the continent be brought about.

No longer the revolutionist, he was always the reformer. Trained as a pathologist to find the abnormal and the diseased, with wits sharpened to peer into the hidden recesses of nature, Virchow could be depended upon to find the sunspots where others saw only the golden radiance of promise. But despite this sober skepsis and his philosophic acceptance of an empiric realism, Virchow was all his life a passionate idealist. Convinced of the fundamental benevolence of human nature, he was sure that all our ills were due to ignorance and the inability or rather the unwillingness of the mass to think. "Science," he wrote, "frees with every step of its advance. Science and knowledge alone permit the individual to be true to himself in the larger sense of the term, for in the measure that he learns to think, as larger and larger fields of knowledge become open to him and more and more objects come into his conscious sphere, in that degree will his ethical demands increase, and we may well hope that the advance of knowledge will entail an ever advancing plane of moral and ethical motivation, will form the well spring of ever greater effort at truth, honesty and faithfulness in human relations." He must truly have been an incorrigible idealist to write this in his sober old age.

But when we once grasp this idealism we can understand his untiring and continuous effort in the service of public enlightenment and education, of public welfare and sanitation, of politics and public administration. It forms the basis of his whole long public activity; his unceasing, untiring effort for the welfare of the people.

Perhaps one short illustration will make apparent why Virchow had so firm a hold on the imagination of common, every-day constituents. How the scientist mastered the science of being a good politician. It was during Schleich's service in the Institute and he relates the story in his biography. Together with Virchow, already an old man, he was working in one of the upper floors of the building when a big redfaced man, dressed in his Sunday regalia of black suit and high silk hat, rushed in upon them, highly excited and indignant. He wished to speak to Virchow, knowing him, as he stated, from having heard him address the meetings of his trade associations. He explained that his wife had died, that the body had been posted at the Institute and that he had now come to bury the body. Going to the morgue in the basement he had found the coffin, but instead of finding the body of his deceased spouse, he had discovered a burly man snoring softly in the luxury of the white satin pillows.

Virchow and Schleich rushed down the stairs and found that the autopsy diener, beautifully drunk on laboratory alcohol, had tossed out the rightful occupant and now lay sleeping off the effects of the jag in the comfortable berth. They threw him out in turn, Virchow kicking him awake for good measure, and replaced the body of the woman.

Then Virchow drove off with the butcher and that afternoon sat at the side of the husband through the long funeral service, drove with him to the cemetery and so spent five hours atoning for the injury that had been done the man. Never was he too busy to be kind to the man below; truly a chivalrous character.

Oct. 13, 1924.

THE INFLUENCE OF HYPERCHOLESTERINAEMIA ON EXPERIMENTAL TUBERCULOSIS OF THE RABBIT

RICHARD H. JAFFE
AND
S. A. LEVINSON

The epitheloid cells of the tubercles in experimental hypercholesterinaemia are filled with double refracting cholesterol compounds, like the reticulo-endothelial cells from which they are derived. The accumulation of the lipoid is limited to the living tuberculous tissue. With the onset of degeneration, the anisotropic fat disappears, to be replaced by isotropic fat, giving the microchemical reactions of neutral fat. In the necrosis, only a few double refracting crystals are found.

The tuberculous cells, in spite of the lipoid droplets in their protoplasma, phagocyte and destroy tubercle bacilli. Therefore these cells cannot be called degenerated cells.

The histiocyte, transformed into the epitheloid cell, retains some of the functions of the original cell. It is still able to take up cholesterol esters as fluid crystals when the surrounding tissue fluid contains an excessive amount of this lipoid.

The oversaturation of the body of the rabbit with cholesterol does not protect the animal against tuberculosis.

Oct. 13, 1924.

TISSUE CULTURES OF MAMMARY GLAND

ALEXANDER MAXIMOW

Fragments of the rabbit mammary gland were cultivated in rabbit blood-plasma with various tissue extracts in different combinations. Bone-marrow

extract was most effective and always produced hypertrophy, proliferation, and anaplasia, the epithelium forming solid strands, irregular cell groups, or single elements, penetrating out of the opened ducts into the growing connective tissue and fibrin. In combination with other extracts, this action of the bone-marrow extract always dominated. In several cases the formative stimulation of the bone-marrow extract on the epithelium produced an exact histologic duplication of a carcinoma. The epithelium underwent complete anaplasia. Enormously hypertrophied, spherical, polyhedral, or fusiform ameboid elements invaded the peripheral connective tissue singly, in spherical or elongated solid nests, or long branched strands. Liquefying the adjacent medium, they formed a pure culture of intensely proliferating, atypic epithelium, scattered over a large area. Irregular and multipolar mitoses, amitoses, fusion to epithelial giant cells, pearl formation with cornification, and various types of degeneration were observed. The proliferating epithelial cells also invaded the dense fibrous interstitial tissue of the explant, producing typical epithelial cell nests, as observed in squamous cell carcinoma of the mammary gland.

Oct. 13, 1924.

PARTIALLY HEALED SPONTANEOUS RUPTURE OF THE AORTA

T. A. NORDLANDER

From the Pathological Laboratory of Rush Medical College

Healed or healing spontaneous ruptures of the aorta are not observed commonly postmortem. Chiari [1] mentions histologic studies of four, all of which occurred in the ascending portion of the aortic arch. In none was there a mesaortitis, although one had a chronic deform-

1. Chiari: "Ueber die Differenz im Mikroscopischen Befund bei Ausgeheilten Aortenrissen und bei sogenannten 'spontanen' Aorten aneurysmen" . . . Verhandlung der Deutsche "Pathologische" Gesellschaft, Jena, 1904; also Centrallblatt für allgemeine Pathologie und Pathologische Anatomie, Jena, 1904, XV, p. 549.

ing endarteritis, which, however, did not involve the part ruptured. In two there was clinically an aortic insufficiency. A fifth, reported later by Chiari,[2] also occurred immediately above the sinuses of the aortic valves. In this instance the aorta was normal, otherwise. The tear extended through the intima and media only. Ernst [3] reports another, quite similar to the ones mentioned, which occurred in the ascending portion of the arch. The intima and media were involved, the elastic fibers of the latter being torn, and only adventitia remained where the wall had been torn. Patoir and Leclercq [4] give a detailed description of a partially healed spontaneous rupture of the aorta. Externally, the wall was unchanged. Internally, there was a band of scar tissue encircling the aorta immediately above the heart valves. The intima at the lower border of the scar formed pendulous tags of tissue resembling supplementary aortic leaflets. A few centimeters above the scar there was a second similar partially healed scar, triangular in shape. Microscopically, endothelium in the region of the scar was absent. There was an hypertrophy of the intima, a granular change of the elastic elements, and a hyaline degeneration of the connective tissue fibers.

There are two photomicrographs of healed aortic tears by C. Benda in Aschoff's "Patholigische Anatomie," 2nd edition, Volume II, pp. 56-57, and also a general discussion of healing in blood vessels.

Violent muscular exertion, or any factor causing a sudden undue rise in blood pressure are given as the general etiologic features. In some instances, as in the "Flieger-Tod" described by German military investigators, they are the only detectable causes. Death in these instances follows a swift, prolonged descent and postmortem examination reveals a rupture in an otherwise normal aorta. Any disease of the aortic wall predisposes to rupture.

2. Chiari: "Praparet eines gehalten Aortenrisses," Deutsche Medizinische Wochenschrift, Berlin, 1914, XL, pp. 1882.
3. Paul Ernst (Zurich): "Geheilte Zirkulare Aortenruptur am Isthmus," Centralblatt fur allgemeine Pathologie und Pathologische Anatomie, Jena, 1904, XV, p. 548.
4. Patoir et J. Leclercq: Un cas de rupture spontane de l'aorte,' L'Echo Medicale, Jan. 8, 1911, XV, No. 730, pp. 13-18.

It is surprising that in some instances of healed ruptures of the aorta, there is no record of clinical manifestations at the time that the vessel probably tore. The individual is entirely ignorant of any change in his physical condition.

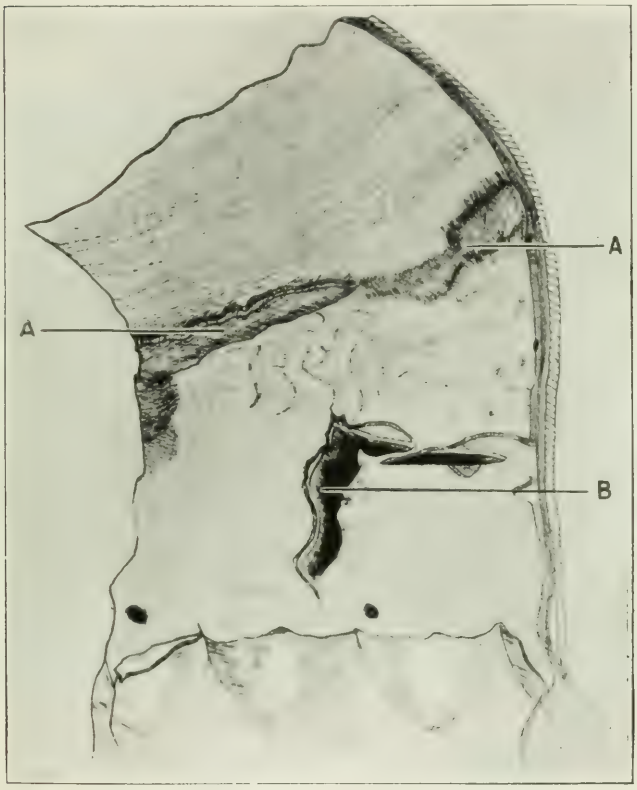


Fig. 1.—*A*, healed rupture; *B*, fatal rupture.

Generally speaking, the different reports do not discuss the origin of the connective tissue in the scar. Borst thinks that it originates from the endothelium. Von Marchand, however, believes that it grows from connective tissue in the vessel wall. It is probable that

both tissues are concerned in the repair. Maximow [5] has recently seen fibrous tissue developing from endothelium cultured in vitro.

No clinical history of this patient is available, inasmuch as death occurred from a complete aortic rupture while the man was at work, and the body was brought directly to the Cook County Morgue. The man was a negro, thirty-four years of age.

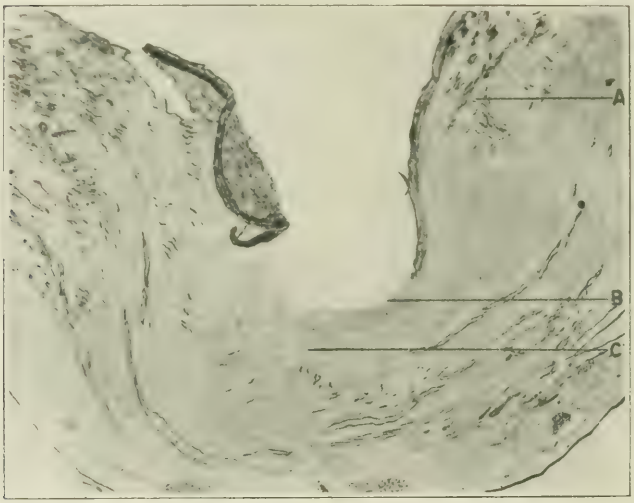


Fig. 2.—*A*, torn elastic fibers; *B*, intima absent; *C*, fibrous tissue.

The anatomic diagnosis (Dr. E. R. Lecount):

Marked syphilis of the aorta; ruptured dissecting aneurysm of the intrapericardial portion of the aorta; huge hemopericardium; depressed liver; passive hyperemia of the lungs, stomach and bowel; slight acute right hydrothorax; slight acute ascites; edema of the brain and leptomeninges with slight anemia; superficial abrasions of the front of the right leg, nasal septum and left buttock; slight hyperplasia of the spleen and mediastinal lymph glands; healed spontaneous

5. Alexander A. Maximow: "Tuberculosis of Mammalian Tissue in Vitro," Journal of Infectious Diseases, 1924, Vol. 34, No. 6, pp. 549-584.

rupture of the root of the aorta; fibrous periaortitis; slight disseminated focal atrophy of the cerebral cortex; necrotic parietal fat tags of the peritonem; fibrous epicardial patches; fibrous obliteration of the left pleural cavity; fibrous adhesions between the left lobe of the liver and the diaphragm; coal-pigmentation of the lungs and peri-bronchial lymph glands.

Macroscopic Description: The pericardial sac is blue and enlarged to 21.5 by 14.5 in its two greatest dimensions. The

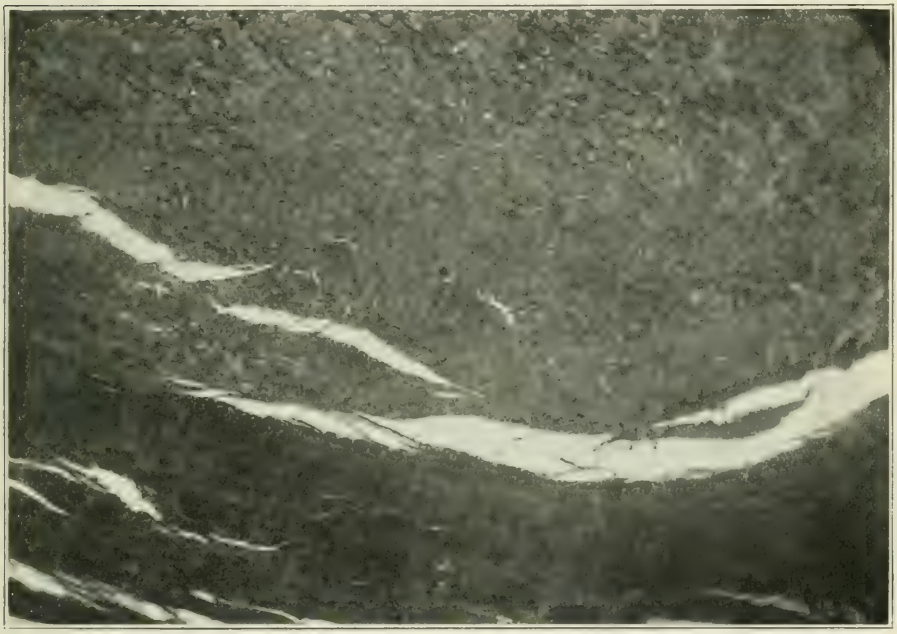


Fig. 3.—Photomicrograph.

most ventral part of the pericardial sac is thinned. Most of the blood in the pericardial sac is clotted loosely. It is slightly adherent to the front of the aorta at the base close to the tear. The intrapericardial blood weighs 979 gms. The anterior portion of the aorta within the pericardial sac is markedly distorted by syphilitic change. The heart is large and the apex is chiefly left ventricle. The lining of the pulmonary is smooth and unchanged. The ductus arteriosus

is closed. The pericardium is bound by fibrous adhesions to the arch of the aorta and in these adhesions are many small tortuous blood vessels. The mitral ring admits four fingers easily. The myocardium is firm and pale. The cavity of the left ventricle is enlarged and rounded more than usual. Externally the rupture in the aorta is 22 mm. long along the course of the aorta—and 18 mm. wide. Internally the rupture is more extensive, and involves the intima and media. It forms a right angle. The longer leg begins a few millimeters to the right of and above the junction of the right and posterior aortic cusps and extends upward along the aorta 37 mm. The other leg extends from here, transversely to the right for 37 mm. (see picture). The edges of the tear are jagged. The adventitia is separated from the media and forms a small aneurysmal sac about 1.5 cm. in diameter.

Beginning close above the left coronary orifice is a depressed band of scar tissue. It extends upward along the aorta 30 mm. and merges into a similar band of scar tissue which encircles the aorta (see picture). In its widest portion this band is 16 mm. Its edges are definite, especially in the transverse portion. It is depressed, approximately 1 to 2 mm. deep.

At the root of the aorta and in the ascending portion are several small regions of fatty change.

Microscopic Examination: Longitudinal sections of the aorta made through the partially healed rupture were stained with hematoxylin and eosin, and with phosphotungstic acid-hematoxylin. In them, there is a sharp break in the continuity of the intima and most of the media for a distance of 0.5 to 1 cm. The intima is intact on each side of the tear, but is absent in the depression where there is healing. In place of the intima and media there is an interlacing meshwork of regenerated connective tissue. This extends into the wall of the aorta almost to the adventitia, being separated from the latter by a few parallel elastic fibers. In this scar tissue are many small angular cells from which extend slender fibrillae. Along the borders of the tear, the elastic fibers are present only as fragmented and torn shreds. Fibrous tissue is present between these masses of torn elastic fibers. In the adventitia are a few focal, indefinitely circumscribed regions which contain many small round cells. These regions are not involved in the tear, and the adventitia appears normal otherwise.

November 10, 1924.

THEORIES ON THE MECHANISM OF BACTERIAL AGGLUTINATION

I. S. FALK

Department of Hygiene and Bacteriology of the University of Chicago

Since 1890, it has generally been recognized that there is an essential identity in the mechanisms involved in the precipitation and agglutination reactions. This is true whether bacterial or non-bacterial reagents are used. The useful application of the reactions in the medical sciences has gone forward regardless of failures to analyze the kinetics of the reactions. Studies of the kinetics have been focused upon the problem of colloid agglutinations.

It has commonly been recognized that a theory of agglutination must account for the reactions produced by acids, alkalies, neutral salts, normal and immune sera, for the "pro-zone" phenomena, and for the differences in agglutinability of different strains of bacteria of the same and of different species. Most difficult of all has been the necessity of accounting for the "specificity" of serum agglutinations and precipitations.

Serum "agglutinins" are commonly removed from sera by precipitation of the globulin fraction. It is alleged that the "agglutinins" have the same isoelectric point as serum globulins. But, according to Went, complete removal of globulins does not result in the complete removal of "agglutinins." "Agglutinins" simulate globulins in their relative stability to trypsins. The relative thermal lability of "agglutinins" has been difficult to explain.

From an analysis of the theories of Bordet and his colleagues; Mansfield; Hirsch; Buchanan; Northrop and De Kruif; Winslow, Falk and Caulfield; Shibley; Green and Halvorsen; Mellon, Hastings and Anastasia; Eggerth; Coulter; Freund; Oliver, etc., it appears that no adequate theory has been proposed.

From an analysis of data on the serum, acid and salt agglutination of a large number of bacterial species, it

appears that a large number of observations are in accord with a modification of the theory originally proposed by Jevons. The electrophoretic potential difference is considered a measure of the force of mutual repulsion between the particles in a suspension. In the absence of a P. D. the surfaces of the particles must of necessity display an aggregating tendency which is inversely dependent upon the surface potential for its magnitude. P. D. and what has been called "cohesive force" are dependent variables. Fewer experimental observations are in disaccord with these views than with any other that have been proposed.

November 10, 1924.

INFECTION AND RESISTANCE IN TRYPANOSOME INFECTIONS

W. H. TALIAFERRO

Blood infections with trypanosomes are found in almost every group of vertebrates. In most cases, when they occur in wild animals under natural conditions, they are nonpathogenic, but when introduced into man or domestic animals, they are almost invariably lethal to their host. The question arises, what is the basis for this difference? It seems logical to suppose that a given species to be nonpathogenic indicates that a higher grade of resistance has been built up against the parasites than in the case of the pathogenic species.

In this work resistance includes all conditions adverse to the life of the parasite after the parasite has successfully invaded the host. Such a resistance may be measured roughly by making daily number counts of the parasites, for if the number of parasites increases at a uniform rate throughout the infection we know that no resistance is operative, whereas if it either remains constant or decreases we know some type of resistance is operative. This effect on the numbers, however, may be brought about by one or both of two factors; the

rate of reproduction of the parasites may be retarded or the parasites after they are formed may be destroyed as the following equation shows:

(1) Number of parasites in the blood at any time	=	(2) Number produced by reproduction	—	(3) Number destroyed	

The first factor is represented by the second term of the equation, the second factor by the third term of the equation. If we can get a measure of any two members of the equation, we can evaluate the third and hence ascertain which factors in resistance were operative. In my work, I have gotten a measure for the first two. The first term is easily obtained by making daily determinations of the number of trypanosomes per cubic millimeter of blood by ordinary blood counting methods. In obtaining a measure of the second term, I have devised an indirect measure of the rate of reproduction of the parasites (which is independent of the number destroyed) by comparing the *variability* in total length of samples of trypanosomes taken at regular intervals throughout an infection. The rationale of the method is based on the well-known fact that any population of animals which is undergoing rapid reproduction will be much more variable in size than a non-reproducing population consisting only of adults. Thus, samples containing only adults (not reproducing) would show a low variability, whereas a population of all ages (reproducing) would show a high variability.

With such methods at our disposal to differentiate the factors in resistance we have examined various pathogenic and nonpathogenic trypanosome infections with the following results:

The rat develops both factors in resistance against the nonpathogenic *Trypanosoma lewisi;* one of which is directed toward the inhibition of reproduction—in other words, after an intensive period of active multiplication, the parasites after about the tenth day remain as adults throughout the remainder of the infection—and the other of which is directed toward the destruction of the parasites after they are formed. It is of

interest that I have found the first factor of resistance developed in the rat to be due to a reaction product formed in the blood of the rat. This reaction product, which does not kill the parasites but simply prevents their reproduction, emphasizes, as far as I know, an entirely new type of resistance of host to parasite and seems to play an important part in the immunity of rats to superinfection and postinfections.

The mouse does not develop any resistance whatever against the pathogenic *T. brucei*. Once introduced, the parasites multiply and increase at a uniform rate until the death of the host.

The guinea-pig develops only one factor in resistance against *T. brucei* and that is directed against the trypanosomes after they are formed and not against their rate of reproduction. In other words, they reproduce at a uniform rate throughout the infection but periodically large numbers of them are destroyed after they are formed.

To summarize, we find that the only difference so far found between a nonpathogenic and pathogenic trypanosome infection is that the host develops, in the first case, a reaction product in its serum which has the peculiar property of entirely inhibiting all division in the parasite, whereas, in the second case, it does not. That type of resistance which is lethal to the parasites after they are formed is found in both pathogenic and nonpathogenic trypanosome infection. Such periodic destructions of the parasites in the pathogenic infections are not effective in eradicating the infection because the few remaining parasites reproduce and make good their losses. In the nonpathogenic infections, however, each periodic destruction of the parasites is so much gained by the host because the remaining ones cannot replenish their numbers by reproduction because of the reaction product which inhibits their reproduction.

Nov. 10, 1924.

ANTIGENIC PROPERTIES OF BACTERIOPHAGE

LLOYD ARNOLD

AND

EMIL WEISS

From the Department of Bacteriology, Pathology and Preventive Medicine, Loyola University School of Medicine, Chicago

D'Herelle [1] believes that the phenomenon of bacteriophagy is produced by a bacteriolytic ferment-like substance secreted by a microbacterium (Bacteriophagum intestinale d'Herelle, 1918). If this ultramicrobic parasite of the bacteria is killed, the bacteriophagic substance cannot be regenerated.

We have pointed out the similarity between the lysin-antilysin, or the bacteriophage-antibacteriophage reaction and those of toxin-antitoxin as well as those of ferment-antiferment nature.[2] We have repeated d'Herelle's experiment. The time of contact between the bacteriophage and alcohol was varied from three hours to seven days. The same concentration of alcohol was used. The precipitate was redissolved in one half and also in equal amounts of salt solution (0.85 per cent.), as compared to the original bacteriophagic substances instead of the broth tube method.[3] The alcohol precipitate redissolved in salt solution had all of the properties of the original bacteriophage. It produced lysis; this lysis was transmissible and increased in power during transmission through susceptible bacteria. The lytic activity of the alcoholic precipitate was inhibited or neutralized by bacteriophagic antiserum. The precipitate, used as an antigen, produces antilysins that neutralize the lytic activity of the soluble alcoholic precipitate as well as neutralizes the phagic activity of the original bacteriophage.

1. The Bacteriophage, Baltimore, 1922.
2. Abstr. of Bacteriol., 1924, 8, p. 28; Jour. Infect. Dis., 1924, 34, p. 317; ibid., 1924, 35.
3. Jour. Lab. & Clin. Med., 1923, p. 720.

Bacteriophage treated with nine parts of alcohol yields a precipitate that is soluble in normal salt solution. This extract has all of the properties of the original bacteriophage. The lytic power of the precipitate can be increased by passage through susceptible bacteria; the antilysins produced after animal inoculation of the extract of the alcoholic precipitate are the same as those produced as a result of bacteriophage injection; heat inactivation is the same for both the precipitated lysins and the original bacteriophagic lysins. We have been unable to substantiate the claim that the active principle causing the phenomenon of bacteriophage is an ultramicroscopic parasite.

Extracts in salt solution of alcohol precipitated bacteriophage show all the properties of the original bacteriophage; the alcohol precipitated bacteriophage can be regenerated; it is transmissible, and it produces the same antibodies.

Heat inactivated bacteriophage produces antibodies just as unheated bacteriophage does, showing in this way a "toxoid" alteration similar to toxins and lysins. This inactivated bacteriophage neutralizes antibacteriophagic serum, demonstrating the presence of a toxophore and haptophore group.

Antibacteriophagic bodies are salted out from the antiserum with the euglobulin fraction.

Nov. 10, 1924.

THE *p*H LIMITS OF GROWTH AND THE REACTION CHANGES PRODUCED IN MEDIUMS BY COCCIDIOIDES IMMITIS

WARNER S. BUMP*

From the Pathological Laboratory of St. Luke's Hospital

Because of the plausibility of some vegetable intermediate host being necessary for the natural life-cycle

* The John Jay Borland Fellow in Medicine.

of Coccidioides immitis, a study of the growth limitations of the mycelial form of the organism is made.

The following are the conclusions based upon the observations recorded [1]:

1. The mold, Coccidioides immitis, grows well on the simplest of mediums, requiring only a small amount of nitrogen for growth.
2. It is an obligate aerobe for growth in the mycelial form.
3. It does not belong to the group of nitrogen-fixing organisms.
4. It grows well in mediums with the great *p*H variation of from 2.02 to 12.13 and therefore can easily withstand the extremes of *p*H change in the soil.
5. It does not by its growth ferment dextrose, lactose, saccharose, or maltose.
6. Ammonia is a product of its growth, greater amounts being formed in the more acid mediums until a critical point (*p*H 6) is reached.

Dec. 8, 1924.

DISSEMINATED NODULAR HYPERPLASIA OF THE LIVER FOLLOWING ACUTE YELLOW ATROPHY

A DEMONSTRATION

E. R. LeCOUNT

From the Pathological Laboratory of Rush Medical College

Dr. LeCount presented a liver sent him for examination by Dr. Frederick Epplen of Spokane, Wash., who obtained it by a postmortem examination of the body of a young man who died at the age of 22 years.

Five years before death the man had become jaundiced, and this never cleared up altogether, although less marked at intervals. There were frequent bowel movements, weakness, swelling of the feet, and for the last two months of life, ascites, marked jaundice and

1. A complete report is published in the Journal of Infectious Diseases.

dyspnoea. There was no pain until the final two or three days of life, when it was severe and general in the abdomen; tenderness of the abdomen and a high fever appeared at the same time.

At the necropsy a generalized acute serofibrinous peritonitis was found, with large masses of fibrin, a moderate jaundice, slight anasarca, considerable fluid in the left pleural cavity, petechial hemorrhages in the dorsal part of the epicardium, in the visceral pleura of each lung and peritoneum covering the pancreas, the spleen six or seven times its normal size with some increase of stroma and passive hyperemia, the stomach dilated and its lining with an état mamelonné of productive chronic inflammation.

At the necropsy no estimates of weights were made. The body was that of an unusually tall man, over 6 feet. The front edge of the liver was above the costal margin the width of three fingers.

The liver (demonstrated) has been in formalin for some time and, although small, weighs 1,530 grammes. Its largest dimensions are 22 x 17 x 12 x 9 cm., the last two being the thickness front to back of the right and left lobes respectively.

Externally most of the nodules project dorsally from the right lobe and ventrally from the left. The largest is near the front edge of the right lobe, 8 x 6 cm., and grown out so as to project from the general liver level 4. It is just to the right of the groove for the gall bladder and dorsally fuses with another outcropping nearly as large at the site of the impressio duodenalis. Such gross outgrowths are all made up of coalescent smaller nodules, although this is not as apparent externally as on surfaces made by cutting. The projecting nodules overlie the adjacent liver tissue in places so that crevices several millimeters deep occur between them.

On surfaces made by cutting, something resembling a pattern is present in the nodules, units of structure or primary nodules from 4 to 10 or 12 mm. in diameter, and these possess in common: scalloped sharply-demarked edges; a deep green color from bile retention, slightly mottled with paler green or gray-green,

and about and between them something resembling narrow fibrous bands. These smaller unit-nodules, if such a term be allowable, are set together closely and compose the larger masses, such as those which project from the dorsal surface of the right lobe. Fused with one another, they project also from the front of the left lobe as a thick plaquelike mass beset with shallow, short furrows and pits. These unit-nodules occupy fully one half of the right lobe and are mainly coalescent and dorsal. In the left lobe they are more discrete.

The tissue between the nodules is not stained with bile and for the most part is devoid of anything which even with a hand lens resembles lobule markings.

Dec. 8, 1924.

STRATIFIED SQUAMOUS CELL CARCINOMA OF THE BODY OF THE UTERUS

EDWIN F. HIRSCH

From the Pathological Laboratory of St. Luke's Hospital, Chicago

Three carcinomas of the fundus of the uterus containing stratified squamous epithelium are reported. The origin of these cells in the fundus is discussed.

The complete report is published in the *Archives of Surgery*, December, 1925, **11**:957-964.

December 8, 1924.

TISSUE CHANGES AFTER EXPERIMENTAL DEEP ROENTGEN IRRADIATION

ANATOLE KOLODNY

ABSTRACT

The histological changes in the liver, the kidneys, the spleen and the intestinal tract following deep seated Roentgen irradiation and the influence of Roentgen

irradiation on the coagulability of blood were studied experimentally on rabbits. The results led to the following conclusions:

Experimental intensive deep Roentgen irradiation produces definite anatomical changes in the liver, the kidneys, the spleen and the intestines, which play a certain rôle in the etiology of radiation toxemia.

The main features of these histopathologic changes are:

1. A destruction of lymphocytes, which is especially prominent in the spleen.

2. A disintegration of erythrocytes in all the organs studied with abundant hemosiderin formation in the reticuloendothelial apparatus of these organs.

3. Degenerative vascular changes with subsequent thrombosis of the vessels.

The destruction of lymphocytes and the disappearance of the Malpighian follicles in the spleen with the overgrowth of the reticular elements of the splenic pulp are the biologic basis for the increase of the coagulability of blood after irradiation.

Dec. 8, 1924.

THE PATHOLOGY, BACTERIOLOGY AND IMMUNOLOGY OF A CASE OF GENERALIZED TORULA INFECTION

B. Z. RAPPAPORT
AND
BERTHA KAPLAN

A complete report is published in the *Archives of Pathology*, May, 1926, **1**:720-741.

January 12, 1925.

THE FRACTIONATION OF AN IMMUNE SERUM BY ELECTRODIALYSIS

ARTHUR LOCKE*

From the Pathological Laboratory of St. Luke's Hospital, Chicago

The immune substances of immune serums are associated with their proteins. The ultimate isolation of the immune substances entails the fractionation of the immune serum proteins, discarding those proteins which are inert and further fractionating those with which considerable immune activity is associated.

It is very possible that all of the *pure* proteins are little soluble in *pure* water. They remain suspended in solutions such as blood serum by virtue of the presence in those solutions of stabilizing inorganic ions. Some of the proteins require the merest trace of salt or of carbonic acid to remain in solution. So that a method of progressive salt removal from a protein solution such as blood serum affords a method for the separation of the protein groups from one another. The method is equivalent to a process of fractional crystallization where the solubilities of the components are gradually reduced by salt removal instead of by cooling. And, as in crystallization, each fraction must be re-flocculated several times before it can be purified from its easily absorbed neighbor proteins.

Simple dialysis is capable of removing traces of salt from protein solutions only with infinite slowness. It is necessary to draw out the ions by electrolysis. The apparatus which Dr. Hirsch and I have improved and simplified for this purpose consists of two dialyzing thimbles supported within a small beaker and provided with water circulation and carbon electrodes. The serum is placed in the beaker, and the dialyzing water circulates within the thimbles. In addition, an electric current passes between the two carbon electrodes, pulling the ions from the serum through the thimble walls to where they can be washed away.

* Seymour Coman Fellow in the Application of Chemistry to Medicine, The University of Chicago.

It is difficult during the process of electro-dialysis to keep the serum from becoming so acid that proteins, and especially the immune proteins, are denatured. We have found that this may be prevented either by a preliminary five-fold dilution of the serum or by the circulation of a solution of calcium bicarbonate, tap-water, through the dialyzing thimbles. Heat denaturation due to the use of too high a current drop has also to be avoided.

A fractionation process equivalent to recrystallization, employing the principle of electrodialysis exclusively, is very tedious and presents no particular advantage over simpler methods of isoelectric separation.

TABLE 1. *The Stratification of the Serum Proteins During Electro-Dialysis*

Sample	Volume in C.c.	Titer. Units per C.c.	Nitrogen Milligrams per C.c.	Nitrogen Milligrams per Unit
Original serum.....	47	666	11.2 ± 5	0.017
Clear layer	26	7	10.0 ± 5	1.4
Middle layer	13	1,300	11.0 ± 5	0.008
Bottom layer	8	1,800	19 ± 1	0.011

But in improving and simplifying the apparatus for the electrodialysis of anti-diphtheritic serum as patented by the German Elektro-Osmose Gesellschaft, we eliminated the continuous stirring of the serum and were at once struck by the phenomenon of stratification which ensued in the serum. Because they lower surface tension, proteins accumulate in the liquid surface and bind electrolytes to that surface. Consequently the electric conductance is greater there and the flocculation of the surface globulins is more rapid. There commences a downward clearing in which the proteins which most strongly influence the surface tension, and they are the immune proteins, go down the fastest.

As an example, tabulated in the accompanying tables, the beaker is filled with a serum containing 666 units of rabbit anti-sheep red cell hemolysin to the c.c. This serum was bled from rabbits which had been injected

intraperitoneally ten days previously with a suspension of washed sheep cells. The hemolytic unit is that volume of the serum which is just sufficient to completely hemolyse 0.5 c.c. of a 5 per cent. sheep cell suspension in the presence of complement. Each hemolytic unit is associated with 0.017 mg. of nitrogen, which was determined by the micro-Kjeldahl method. After six hours electro-dialysis against tap-water at a voltage rising from 18 to 25 volts, the top zone of 26 c.c. contains only seven hemolytic units to the c.c., one unit associated with 1.4 mg. of nitrogen. An intermediate zone of 13 c.c. contains 1,300 units to the c.c., one unit associated with 0.008 mg. of nitrogen, and the bottom layer

TABLE 2.—*The Progress of the Fractionation*

Stage of the Fractionation	Milligrams of Nitrogen per Unit
Original serum	0.017
After stratification	0.008
After loss of euglobulin and albumin	0.004
After restratification, flocculation and drying	0.0008
Distilled water extracts of "sensitized" stroma as discussed in text	0.00006

contains 1,800 units to the c.c., one unit associated with 0.011 mg. of nitrogen. The central and bottom layers contain considerable inert euglobulin which precipitates when the solution is diluted. The central layer already illustrates a fractionation from 50 per cent. of the serum protein.

The intermediate layer is further electrodialysed against distilled water, after removal of euglobulin, when a sticky gum is obtained upon the bottom of the beaker of such potency that one unit is associated with only 0.0008 mg. of nitrogen. This gum may be dried and preserved with negligible loss in potency.

This gum represents even yet a highly impure preparation of the immune hemolysin. We have prepared extracts of sheep-cell stroma which have been allowed to absorb immune hemolysin from a hemolytic serum and have been subsequently washed free from the

serum proteins. These extracts have been reported by others as "protein-free," but have been determined by us to contain as much as 0.00006 mg. of nitrogen per unit. We have flocculated the active material from one of these extracts but not in a sufficiently large and satisfactory sample for comparison with material obtained by direct fractionation of the serum.

In conclusion, I hope that I have made clear the basic principles of isoelectric reflocculation and the advantageous employment of the higher surface activity of immune psuedoglobulin, which have enabled Dr. Hirsch and myself to quantitatively conserve the potency of an immune serum, the rabbit anti-sheep red cell hemolysin, while concentrating to a value of only 0.0008 mg. of nitrogen per unit.

Jan. 12, 1925.

STUDIES ON EXPERIMENTAL AMYLOIDOSIS

RICHARD H. JAFFE

Experimental amyloidosis can easily be produced in mice by repeated intramuscular injections of nutrose (sodium caseinate). The beginning of the amyloid degeneration can be observed after 40-70 injections, the organ first affected being the spleen. Later, amyloid appears in the liver, kidneys, adrenals, intestine, pancreas, gallbladder, heart and ovary.

The amyloid gives the three microchemical reactions typical of this substance, and it often forms radiar-fibrillar structures resembling crystals. In the liver, the amyloid may become dissolved or phagocyted by proliferating endothelial cells, though the injections are continued.

The amyloidosis is explained by the coincidence of an excessive protein cleavage with an increased capillary permeability.

Jan. 12, 1925.

TRUE CHOLESTEATOMA OF THE CAECUM

CHARLES E. HUMISTON
AND
EUGENE C. PIETTE
From the West Suburban Hospital, Oak Park, Ill.

A complete report is published in the J. A. M. A. March 21, 1925, **84**:874-876.

February 9, 1925.

PAROVARIAN CYST OF UNUSUAL SHAPE (PERSISTENT WOLFFIAN DUCT?)

EUGENE C. PIETTE, M.D.
From the West Suburban Hospital, Oak Park, Ill. Read before Chicago Pathological Society

Although the rests of the embryonic structures—epoophoron, paroophoron and appendix vesiculosa of the tube—are often present in the region of the ovary, we found no complete description of their normal appearance. As to the pathology of these formations very little is known. That is the reason for reporting our case, where a cyst of quite unusual form was found in the abdominal cavity, being associated with the ovary. We were unable to find any similar case in the literature. The history is as follows:

Miss E. D., white, aged 23 years, patient of Dr. Woof, was admitted to the West Suburban Hospital September 25 with a diagnosis of "subacute appendicitis." She had an attack of abdominal pain in June and then another attack a week before admission. Menstruation regular, the last period being August 26. Examination was negative except for a tenderness over McBurney's point.

Operation was performed by Dr. Woof on the same day. Appendix was removed and also a large cyst attached to the

Fig. 1.—Gross appearance of the cyst.

right ovary with a thin pedicle. Postoperative course was normal, and the patient left the hospital October 4.

Grossly the thin sac is transparent, has the form of a spindle and in profile is roughly crescentic. It measures 18 cm. in length and 2 cm. in its widest diameter. The wall is about 0.1 of a millimeter thick, is thrown into irregular rather deep folds and has no visible blood vessels. No pedicle is present so that

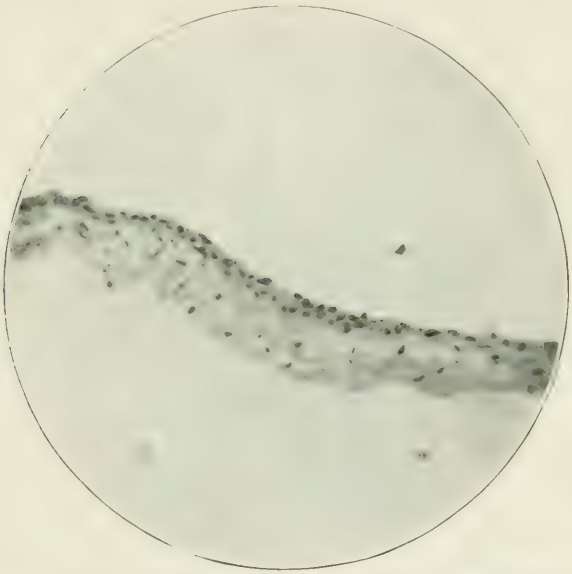


Fig. 2. Wall of the cyst under high dry power. Note absence of the vessels.

the impression is given that it was loose, or that the attachment is small, but independent of any communication with an abdominal viscus.

The fluid content of the sac is clear, watery, showing no formed elements in the hanging-drop preparation and only traces of albumin on chemical examination.

In paraffin sections the cyst wall is seen to be made up of thin collagen fibers lined by two or three inner sheets of flat cells. The serous covering is absent,

probably being lost in handling, since the cyst was delivered to the laboratory in a gauze dressing. Although similar formations associated with the ovary, such as the paroophoron, epoophoron and appendix vesiculosa usually have a distinct vascular supply, no vessels were to be found in the cyst wall even after careful search. The absence of vessels, it seems, resulted from a torsion of the pedicle at an earlier stage, the sac being sufficiently thin to be adequately nourished through imbibition of peritoneal fluid.

Fig. 3.—Partial reconstruction of the Wolffian duct (*pH*) and definitive kidney (9 mg.), Schreiner in Hertwig's Handbuch der Entwicklungsgeschichte. Human fetus about 5 weeks old. Note the resemblance of the folded Wolffian duct to the cyst, figure 1.

As to the nature of this cyst it seems permissible to suggest its origin from a persistant Wolffian duct on the basis of similiarity of the shape of the cyst to the reconstructed embryologic models of the Wolffian duct and the folded condition of the wall in both. The difference in the morphology of the cells lining the two structures can be readily explained on the basis of local conditions for it is well known that epithelium can assume various forms according to pressure, or

other factors (prosoplasia). The flattening of the cells lining the cyst is therefore no objection to the assumption that this represents a dilated Wolffian duct.

February 9, 1925.

HISTOPATHOLOGY OF AGRANULOCYTIC ANGINA

EUGENE C. PIETTE

From the West Suburban Hospital, Oak Park, Ill.

A complete report is published in the J. A. M. A. May 9, 1925, **84**:1415-1416.

February 9, 1925.

EVIDENCE OF NERVOUS CONTROL OF LEUCOCYTIC ACTIVITY

E. F. MUELLER

A complete report is published in the *Archives of Internal Medicine*, February, 1926, *37* pp. 268-280.

February 9, 1925.

THE RELATION BETWEEN BLOOD VOLUME AND BLOOD PRESSURE IN ANAPHYLACTIC AND PEPTONE SHOCK*

J. P. SIMONDS

From the Department of Pathology, Northwestern University Medical School

SUMMARY

1. In most dogs there is an evident increase in blood concentration and a reduction in blood volume during anaphylactic and peptone shock.

* The entire paper will appear in the American Journal of Physiology.

2. In a small percentage of dogs there is apparently a decrease in concentration and an increase in blood volume in these conditions in spite of the marked fall in blood pressure.

3. In non-fatal peptone shock the blood pressure regains its normal level before the blood volume is completely restored.

4. Maintaining blood volume at its normal level by the intravenous injection of physiological salt solution does not prevent the fall in blood pressure. Restoring the normal blood volume by the same means does not cause a rise in blood pressure.

Feb. 9, 1925.

CARCINOMA OF ABERRANT THYROID GLAND WITH METASTASIS

A CASE REPORT *

MILLARD T. NELSEN

AND

A. C. IVY

From the Medical Service of Drs. Anders Frick, Augustana Hospital, Chicago

The following case report is given because of its variety, and in possible explanation of some of the bizarre growths and metastasis seen in malignancies of the thyroid, both when the thyroid is involved itself, or in cases where it arises in thyroid tissue completely isolated from the true gland. L. B. Wilson* in reporting 290 cases of malignant tumors of the thyroid mentions one case similar to the following:

Patient J. N., a single male laborer, 68 years of age, entered Angustana Hospital on the medical service with a complaint of pain and tingling throughout arms and shoulders. Three months prior to entrance, he had experienced an attack of sharp pain in region of xyphoid and epigastrium, which later seemed to extend upward into right shoulder girdle and arm.

* L. B. Wilson, Malignant Tumors of the Thyroid, Annals of Surgery, August, 1921, p. 177.

During the past three weeks pain in the left arm has been more constant and severe than in right. He has noticed in the past six months that it is easier to breathe in recumbent than standing posture.

The past history reveals an acute bronchitis and subsequent pneumonia three years ago, with recurrent attacks of pharyngitis for over two years. Usual weight is 170 pounds, but at present 136. He sleeps poorly, but appetite is good. No venereal diseases. He has been deaf for years. The pain in arms and weakness have kept him from work for over one month.

The admission physical examination presents a deaf male in poor nutrition with facial expression of anxiety and concern, and showing evidence of pain on movement or change of posture in bed. The pupils are round, react readily, but left is slightly larger than right. Nose, prominent because of moderately large rhinophyma. Tonsils, cryptic masses, hypertrophied. Thyroid, normal consistence, distinct but not enlarged. Chest, anterior posterior diameter increased with tendency toward barrel shape; no external tenderness; slight dyspnea when sitting up; superficial blanched scars over anterior chest wall as result of previous "electric treatments" three years ago; emphysematous chest with scattered course râles over greater portion with no areas of compression noted. Vascular system negative except for mild brachial and radial arteriosclerosis. Blood pessure 124/88. Extremities, slight clubbing of finger tips.

During the next two weeks there developed a bark-like cough, and profuse watery sputum; severe dyspnea on assuming erect posture, but partly relieved by left recumbent position with head acutely flexed on thorax. This position was maintained almost constantly. The following week an inspiratory and expiratory stridor developed, with gradual loss of strength, profuse sweating, slight blueness of upper half of thorax, neck and face. Percussion showed increased widening of manubrial dullness, more to left of midline than to right. Fluoroscopic examination demonstrated a nonexpansile mass in upper thorax whose left border apparently pulsated, but with right indefinitely fixed.

The irregular pupil, indefinite resistance in jugular notch, the fluoroscopic and percussable mass in anterior upper thorax with progressive respiratory distress, loss of weight and strength, watery profuse sputum, bark-like cough, and two negative Wassermann reactions led to a diagnosis of a malignant tumor of the mediastinum. Operation deemed inadvisable because of patient's condition. Patient died suddenly, preceded

a few hours by an acute gastric dilatation with bloody grumous vomitus, and progressive respiratory distress.

Autopsy: The body is that of a poorly nourished emaciated man of about 65 years of age. The abdomen is markedly distended. Further external examination of skin and skeleton is negative.

The intestines are markedly distended with gas down to the mid-point of the transverse colon, where a band of fibrous adhesions causes an obstruction. On opening the colon proximal to the obstruction it is found that the lumen barely permits the passage of the ungloved little finger. The colon beyond the point of obstruction is empty and normal.

The stomach is markedly distended with approximately 1.5 liters of brown fluid which contains much black coffee ground looking material. No point of hemorrhage is to be found in the esophagus, stomach or intestine.

The kidneys, spleen, pancreas, bladder and prostate grossly appear to be normal.

The liver is not enlarged. Near the edge of the lower right lobe of the liver there is a glandular tumor mass 3 cm. in diameter, appearing to be a metastasis from some primary tumor.

There is approximately 250 c.c. of bloody straw colored fluid in each pleural cavity and 100 c.c. of clear straw colored fluid in the pericardial cavity.

The lungs are emphysematous, hyperemic and edematous, and the trachea is filled with slightly bloody, frothy, sero-mucous material. No nodules are present in the lungs.

The heart and blood vessels are normal.

In the right fifth rib just anterior to the mid-axillary line there is a tumor mass 2 by 1.5 cm. in size that replaces the bony structure of the rib at that point. At this point the rib is fractured—a pathological fracture.

There is an elipsoidal tumor 6 by 12.5 cm. located behind the medial fourth of the right clavicle extending 2 cm. above and 10 cm. below the clavicle. It is closely adherent to the right posterior aspect of the trachea 7 cm. below the cricoid cartilage, at which point the trachea is displaced to the left and is "saber-shaped." The esophagus is displaced to the left and lies posterior to the tumor. The tumor is hard and nodular and does not infiltrate the surrounding tissues. The tumor shows no perforation into the esophagus or trachea.

On section the tumor appears to be composed of glandular, osseous and cartilagenous tissue.

The two lobes and isthmus of the thyroid are of normal size, shape and appearance and have no connection with the tumor mass.

Anatomic Diagnosis: Intestinal obstruction with acute dilatation of the stomach; carcinoma of an accessory thyroid with metastases to the liver and right fifth rib; edema, hyperemia and emphysema of the lungs with a sero-sanguinous exudate in the pleural cavities, serous pericarditis; pathological fracture of the right fifth rib.

Histologic Examination: Sections through the primary tumor shows that it is composed chiefly of parenchymatous tissue surrounded by a dense (1 mm. thick) fibrous capsule. The tissue that was grossly thought to be osseous and cartilagenous on histologic examination proves to be calcified and dense connective tissue. The parenchymatous tissue presents areas with the appearance of normal thyroid with acini containing colloid, of hyperplasia, of foetal adenoma and of carcinoma of the thyroid.

Section through the metastasis in the rib presents the appearance of foetal adenoma and hyperplasia of the thyroid.

Section through the metastasis of the liver presents the appearance of normal thyroid with acini containing colloid, of hyperplasia and of carcinoma of the thyroid.

Section through the normal appearing lobes of the thyroid shows the anatomical normal thyroid to be normal in some areas and slightly hyperplastic in others.

Histologic Diagnosis: Carcinoma of an accessory thyroid with metastases to the liver and right fifth rib.

March 9, 1925.

FOOT-AND-MOUTH DISEASE

L. E. DAY

Foot-and-mouth disease is a disease of bisulcates to which cattle and hogs are the most susceptible, and it is one of the most highly contagious plagues known to science.

This disease has never gained a permanent foothold in the United States, but has been a permanent pest to the live stock industry of Continental Europe and the Orient for centuries.

The United States has been visited by this plague on several occasions. The most noteworthy visitations were in 1902, when the disease spread over a portion of the New England states; in 1908, when the disease

appeared in New York, Pennsylvania, Maryland, Ohio and Michigan; in 1914, when the disease made its appearance in Michigan and spread to twenty-two states before it was controlled. The last outbreak made its appearance in the Bay district of California in the beginning of 1924 and spread to sixteen counties within the state before it was controlled. During September of the same year it made its appearance in the neighborhood of Houston, Texas, where it spread to nine herds, when it was quickly checked.

Up to the present time the causative factor of foot-and-mouth disease has not been fully determined. Loffler and Frosch, Nocard and Roux proved that the virus of the disease will pass through the filters of Chamberlain and Berkefeld, but is partially retained by the denser Kitasato filter. It has not yet been possible to demonstrate the organisms either by staining or by cultivation. The virus therefore must be looked upon as an extremely minute ultramicroscopic micro-organism. About a year ago Frosch and Dahmen, of Berlin, reported that they believed they were able to cultivate the organism of foot-and-mouth disease, but their work has not been fully accepted.

The virus is contained in its purest state in the contents of the vesicles which develop in the early onset of the disease. The blood is also infectious in the early stages of the disease, as well as the various secretions of the body.

In strong healthy animals the first symptoms noticed are rigors, elevation of the temperature to 104-108, and loss of appetite. These prodromal symptoms are soon followed by vesicle formation on the inner surface of the lips, tip and dorsal surface of the tongue, dental pad, muzzle, and commisure of the interdigital space and coronary band of the feet, and frequently the udder and teats. The vesicle formation in the oral cavity is very extensive. The vesicles soon rupture and the mucous membrane sloughs, leaving the inner surface of the lips, dental pad, tip and anterior half of the dorsal surface of the tongue a raw denuded surface. Like changes take place around the coronary band and commissures of the feet. The sloughing is so extensive in

the feet of heavy fat cattle that they occasionally shed their hoofs. Complete shedding of the hoofs in swine is quite a common occurrence.

The period of incubation is very short, ranging from 48 to 72 hours by direct inoculation of the virus under the mucous membrane of the mouth or by intravenous injection, and from two to seven days, occasionally eleven or fourteen days, by natural exposure.

The virus is spread by contamination and may be carried great distances in railroad cars and on the clothing of people. In some instances birds have been known to carry the infection several miles.

The mortality is not high. European writers place it at from 2 to 10 per cent., or even higher, depending on the severity of the outbreak. In the United States we have no accurate figures on which to compute the mortality, as we slaughter all infected and known exposed animals as quickly as possible.

During an outbreak of this disease practically every line of business suffers on account of the strict quarantine that it is necessary to impose to control the spread of the disease. This makes the aggregate loss to the business of the country enormous.

The methods employed to eradicate foot-and-mouth disease in the United States are rigid quarantine and slaughter and burial of all infected and known exposed susceptible animals. While this is a very expensive procedure at the time, it has been proven to be the most economical in the end.

Infected and exposed animals are appraised by disinterested parties. The United States Government pays one half and the state in which the infection exists pays the other half. The animals are slaughtered and placed in a trench at least seven feet deep and covered with quicklime, and the trench is then filled in with at least three feet of earth. All stables, sheds and corrals are cleaned and thoroughly disinfected, and no animals are allowed on the premises for at least sixty days, and most instances ninety days, after disinfection. Test animals are first placed on the premises for sixty days before the farms are restocked. The test animals are

examined daily for a time, then twice a week, until the test period is completed.

Inspectors and others engaged in the work are required to wear rubber clothing when examining infected or exposed animals. After each examination the rubber garments, which consist of a long coat, thigh boots, hat and gloves, are thoroughly sponged with clear cold water to remove every particle of adherent matter, and finally washed with a 1 to 1,000 solution of bichloride of mercury. By this method it has been found that the disease has not been spread from one premise to another by inspectors.

April 13, 1925.

THE PRIMARY CYLINDRICAL CELL CARCINOMA OF THE LUNG

WILLIAM HUEPER
Mercy Hospital

It is well known that the differential diagnosis between tuberculosis and carcinoma of the lung may be difficult. The symptoms and physical findings may be alike. With each there is a purulent sputum, hemoptysis, dyspnea, loss of weight, sweating and fever. As physical signs are dulness, generalized or in isolated spots, harsh breathing, moist and crepitant râles.

Examination with the roentgen-ray may not differtiate. There are shadows in isolated spots and along the bronchi in both.

Sometimes a primary carcinoma of the lung may start from an old tuberculous cavity of the lung, and the presence of acid fast bacilli in the sputum of such a patient may lead to a wrong diagnosis. It is known that the sputum of a patient with gangrene of the lungs may contain acid fast bacilli, which are not tubercle bacilli but only saprophytes. Also a tumor of the lung may cause a gangrenous process by obstruction of a bronchus. Therefore, it is possible that finding of acid fast bacilli in the sputum of a patient with a lung carcinoma may be regarded, together with

the physical and roentgen-ray findings as conclusive evidence of pulmonary tuberculosis.

I had the opportunity sometime ago to examine post-mortem a patient where acid-fast bacilli were found repeatedly in the sputum and who had been treated several months for tuberculosis of the lungs. The resection of several ribs became necessary, because of an empyema or lung abscess and as a result of this operation the diagnosis of carcinoma of the lung was made.

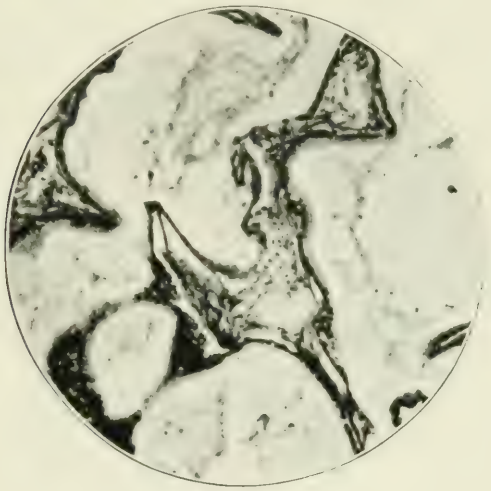


Fig. 1.—Cysts in the pleura.

The pathologic department received for examination tissue from the left thorax, a piece the size of a hen's egg, rather dense with fibrous tissue, and adherent grayish white gelatinous material. Cystic regions filled with opaque mucous material were scattered throughout.

Microscopically, it contained fibrous tissue, fat and striated muscle. An elastic tissue stain demonstrated the elastic membrane of the pleura, split into layers by fibroblasts. There were cysts in the connective tissue layer, lined with columnar or goblet cells and

containing material giving a mucin reaction. There were also papillae. Delicate incomplete connective tissue septa between the cysts indicated a confluence of several cysts. The loose connective tissue around some of the cysts was infiltrated with tumor cells and contained coagulated gelatinous extracellular substance. Adherent to the inner side of this fibrous layer was tissue, that resembled, with low magnification, an emphysematous lung. Thickened connective tissue septa with perivascular round cell infiltration separated the lobules. The delicate alveolar septa were intact and the elastic tissue framework was normal in distribution. The distended alveoli were lined with regular cylindrical cells and, in places, goblet cells. In a few places the normal cuboidal cells remained intact. The lining was always in a single layer, and transitional forms between the high columnar tumor cells and the low cuboidal alveolar epithelial cells were never observed. Papillary growths into the distended alveoli or cysts were frequently seen. These alveoli were distended with a mucous secretion of the lining tumor cells. Desquamated tumor cells were found in the lumen of the cysts, some with two or even more nuclei. The ciliated cylindrical epithelium of the bronchi and terminal bronchioles was well preserved and never displaced by tumor cells. There was always a sharp line of demarcation between the deeper staining ciliated epithelium of the bronchioles and the lighter staining higs cylindrical tumor cells of the alveoli.

The pathologic diagnosis of this tissue was "gelatinous cylindrical cell carcinoma of the lung." But it was impossible to determine whether this tumor was primary or secondary. Tumors of similar structure have been described as primary carcinomas of the lung as well as metastatic tumors derived from a pseudomucinous cystadenoma of the ovary. The postmortem examination demonstrated a primary tumor of the lung. The essential changes noted are as follows:

Mediastinum: Massed and adherent lymph glands on the left side from hilus to aperture of thorax. These were hard and grayish white, on surfaces made by cutting contained many cysts filled with tenacious, white mucus.

Right lung: Negative.

Left lung: Firmly adherent pleura. Lung solid and firm. No normal lung tissue found upon section. The lung was filled with grayish white confluent nodules. Tissue between these nodes had a glasslike translucency and was composed of a delicate network with pin-head and larger sized mucous cysts. A tenacious mucelous exuded from the whole cut surface. The bronchi were uniform in thickness and normal in color. The hilus glands were of the same consistency as the neck lymph glands. There was no trace of tuberculosis in either lung.

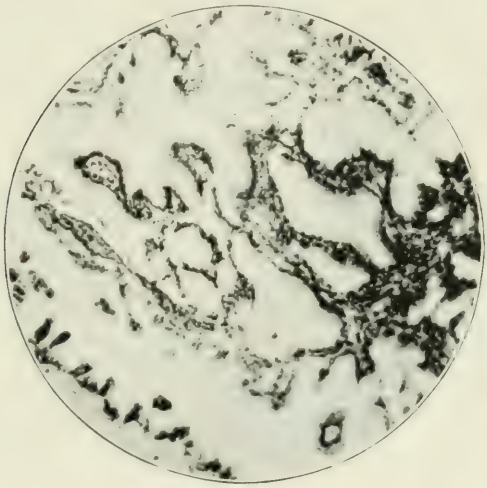


Fig. 2.—Section of the lung.

Abdominal organs: Negative. The ovaries were entirely normal.

Microscopic examination: The histologic findings were the same as those mentioned in the surgical specimen.

The walls of some of the larger bronchi examined showed an invasion of the tumor cells, with complete destruction of the mucosa. The peribronchial lymph spaces and mucous glands were invaded and destroyed by the tumor tissue. The hilus glands were completely replaced by tumor cells. These vary from cysts to single and grouped cells surrounded by mucin.

We considered this tumor to be a primary gelatinous cylindrical cell carcinoma of the lung starting from the alveolar epithelial cells in many centers. The origin from multiple centers was probable because of many nodes in the left lung without the evidence of a primary lesion.

Primary gelatinous cylindrical cell carcinomas of this type are very rare. They were described by Kretschmar, Ribbert, Briese and Gordon. The tumors described by Loehlein and Kelly as benign adenomas of the lung probably belong to this group of carcinomas. The absence of any tuberculosis of the lung demonstrated that finding acid fast bacilli was due to the presence of acid fast saprophytes in the sputum.

Primary lung carcinomas seem to have become more frequent since the last published statistics.

While Ewing states a frequency of 0.1 per cent, Kaufmann of 0.2 per cent, Barron for the years 1919-1921 reports a frequency of 0.9 per cent, Seyfarth even 1.5 per cent for the first half of 1924, and we found in about 5,000 necropsies of the years 1911-1921 in the Auguste-Victoria Hospital in Berlin, thirty-three cases of primary lung carcinoma, or 0.65 per cent.

This increase may be due, according to Hampeln and Seyfarth, to a chronic irritation of the bronchial and lung epithelium by the increased production of smoke and dust in the modern big cities, while Moise thinks that the last grip epidemics with the frequent lung involvement are the cause for this increase.

References

Helly: Ein seltener primaerer Lungentumor, Zetschr. f. Heilk, **28**: 7, 1907.

Loehlein: Cystisch papillaerer Lungentumor, 12. Verhdlg. d. d. pathol. Gesellschaft. **3**, 1908.

Nicholson: Ueber lokale Destruction und multiple Lungenmetastasen beim Pseudonmucikysteom. des Eierstocks, Zeitschr. f. Geburtsh. u. Gyn. **64**: 253, 1909.

Ribbert: Geschwulstlehre. 498, 1904.

Briese: Zur Kenntnis des primaeren Lungenkarzinoms. Frankf. Zetsch. f. Pathol. **23**: 48, 1920.

Kretschmar: Ueber das primaere Bronchial-and Lungenkarzinom. Ing. Diss Leipzig. 1904.

Gordon: Note on Case of Primary Diffuse Alveolar Carcinoma, Lancet, **2**: 501, 1920.

Moise: Primary Carcinoma of the Lung, Arch. Int. Med. **28**: 733, 1921.

Adler: Primary Malignant Growths of the Lungs and Bronchi, New York, 1921.

Kaufmann: Lehrbuch of. spez. Pathol. **367**, 1922.
Ewing: Neoplastic diseases. 785, 1919.
Barron: Carcinoma of the Lung: A Study of Its Incidence Pathology and Relative Importance, etc., Arch. Surg. **4**: 624, 1922.
Seyfarth: Primaere Lungen (Bronchial) Carcinome in Leipzig, Klin. Wchnschr., 1788, 1924.
Hampeln: Haeufigkeit und Ursache des primaeren Lungencarcinoms. Grenzgeb. f. Chir. u. Med. **36**: 145, 1922.
Muir and Ritchie: Manual of Bacteriology, 293, 1913.

March 9, 1925.

AN UNUSUAL CASE OF CARCINOMA OF THE GALLBLADDER

DEMONSTRATION OF SPECIMEN CLINICAL HISTORY

HARRY A. SINGER, M.D.

From the Pathological Laboratory of the Cook County Hospital, Chicago

The necropsy specimen which I desire to present was obtained from a white male aged 49 years, who entered the Cook County Hospital, Feb. 13, 1925, on the service of Dr. C. S. Williamson, and died March 1, 1925. The patient's story of his illness, supplemented by information obtained from his private physician dated back two years, at which time the patient suffered from a severe attack of right upper quadrant pain lasting from six to eight weeks, unassociated with jaundice. For a year or more following the initial attack of pain, the patient was able to carry on his occupation, but was forced to discontinue work after that time on account of abdominal pain, jaundice and weakness. The pain and icterus occurred concomitantly for periods of from five to twenty-one days, at intervals of from three to four months. The present attack of icterus began five weeks before entrance, there being, however, a remission of approximately one week a fortnight before the patient sought admission to the hospital. The pain was no longer a prominent symptom, the patient's chief complaints at this time being jaundice with its associated manifestations and loss of weight and strength. The remainder of the history had no special reference to the immediate morbid state.

The physical examination disclosed in a moderately emaciated, deeply jaundiced individual the following essential abdominal findings:

Tenderness and increased resistance in the right upper quadrant; enlargment of the liver, its lower border reaching to the umbilicus; a sharp firm hepatic edge, but an irregular anterior surface presumably due to nodular prominences.

The temperature was irregular and ranged between normal and 102 F., with a pulse rate that was proportionately rapid. The white blood count was 20,200, 86 per cent of which were polymorphonuclear leukocytes. The red count and hemoglobin indicated the presence of a high-grade secondary anemia. Four stools, the first of which was tarry, all gave a positive chemical test for blood. The stomach and duodenal bulb were normal roentgenologically.

The diagnosis of a carcinoma of the head of the pancreas or of the ampulla of Vater, with associated cholangitic or hepatic suppuration was suggested. An exploratory laparotomy was recommended, but before surgical intervention was undertaken the patient died.

MORBID ANATOMY

The necropsy performed on the day of death demonstrated in the biliary system the interesting condition present in these fresh tissues (figs. 1 and 2). In the region of the bed of the gall-bladder is a deep cavity (fig. 1c), the size of a small orange which is lined mainly by tumor tissue and in part by an irregularly scarred network of fibrous tissue, presenting here the appearance of a healed ulcerative cholecystitis. This excavation represents the remains of the gallbladder which has been replaced for the most part by tumor tissue. Progressive extension into the adjacent liver substance and accompanying necrosis of the tumor tissue has led to the apparent marked increase in size of the lumen of the gallbladder. This cavity communicates with the duodenum (fig. 1d) through an opening 6 cm. in diameter, beginning at a point 3.5 cm. distal to the pyloric ring and terminating 6 cm. proximal to the papilla. The margins of this spontaneous

cholecystoduodenostomy are well healed and free from tumor invasion. The ductus choledochus is not obstructed; it is slightly dilated and contained at the necropsy a mucoid material. In the cystic duct, 1.5 cm. proximal to its anastomosis with the hepatic duct is an impacted biliary calculus (fig. 2bc), which apparently

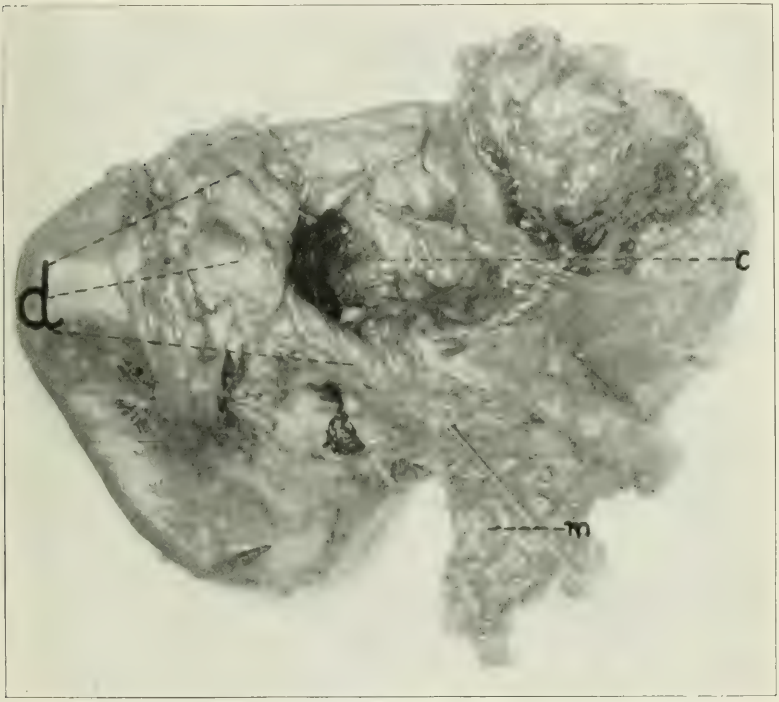


Fig. 1.—The duodenum (*d*) is opened along its lesser curvature exposing a cavity which unites the lumen of the bowel and the excavated bed of the gallbladder. The sound enters the cavity via the ductus choledochus through a perforation in the hepatic duct (Fig. 2, *p*). An implantation metastasis (*m*) is distal to the papilla.

totally obstructs the passage. The neck of the gallbladder has been consumed in the ulcerative process so that a probe passed proximal to the stone soon enters the above described excavation (fig. 2c).

Almost completely encircling the lumen of the hepatic duct and infiltrating its wall 1 cm. beyond the union of its components, is a tumor nodule completely occluding the duct. This flat mass of tumor tissue 2cm. in diameter has a central perforation (fig. 2p) which leads into the same large cavity as that of the cystic duct. By means of this communication a channel for

Fig. 2.—The bile passages are opened from behind. The ductus cysticus (*dc*) is obstructed by a biliary calculus (*bc*) beyond which the duct leads to a cavity (*c*) (cf. fig. 1) which communicates with the duodenum. The probe is passed through the common duct, its termination leading to a perforation (*p*) in a tumor nodule involving the hepatic duct (*dh*). A ridge (*r*) marks the separation of the two biliary channels which form the ductus choledochus.

the liver bile is established between the occluded hepatic duct and the duodenum through the cavity forming the cholecystoduodenostomy. Proximal to the tumor in the hepatic duct there is a marked ectasia of the biliary radicals which are distended by a green mucopurulent secretion. The hepatic tissue is deeply bilestained but

free from frank abscesses. The tumor involvement of the liver is limited to the region adjacent to the fossa of the gallbladder.

The essential pathology is summarized in the anatomic diagnosis in which an attempt has been made to arrange the events in chronologic sequence, based partly on conjecture.

ANATOMIC DIAGNOSIS

Old, extensive ulcerative cholecystitis; calculus obstruction of the cystic duct; functioning, spontaneous, cholecystoduodenostomy; primary, lucerating carcinoma of the gallbladder (microscopically, cylindrical cell type); tumor erosion of the gallbladder and adjacent liver parenchyma with huge cavity formation; carcinomatous obstruction of the hepatic bile duct with perforation into the hepatocholecystic excavation; icterus gravis; cholangiectasis; ascending catarrhal and suppurative (microscopic diagnosis) cholangitis; tumor destruction of the proximal portion of the cystic duct and the neck of the gallbladder; carcinoma extension to the liver; tumor invasion of the upper abdominal lymph glands; localized carcinoma lymphangitis of the mesentery of the small bowel; implantation metastases of the mucosa of the small intestine; tumor adhesion between the hepatic flexure of the colon and the liver; tarry material (altered blood) in the stomach and small intestine; generalized emaciation and anemia. (The remainder of the anatomic diagnosis is not related to the essential pathology.)

COMMENT

The assumption has been made that the original lesion was an ulcerative cholecystitis based on the scarred appearance of a remaining portion of the gallbladder wall. In association with the inflammatory changes biliary calculi were formed, one of which, far too large to enter the cystic duct, was extruded from the gallbladder into the adherent, first portion of the duodenum. That the perforation is not of carcinomatous origin is borne out by the fact that the margins of the spontaneous anastomosis are free from tumor tissue and

have the smooth appearance of a surgical union. The origin of the malignant growth probably followed the cholecystitis and cholelithiasis.

The unique features of the case are first, the fact that the liver bile reached the duodenum without surgical procedures in spite of carcinoma occlusion of the hepatic duct, and second, the unusual route of the bile flow. The obstruction resulting from the tumor nodule in the hepatic duct was probably responsible for the silent jaundice which became noticeable five weeks before entrance. The remission occurred presumably as a result of central perforation of the new growth permitting the stagnant bile to reach the gallbladder cavity and empty from there directly into the duodenum. The recurrence of the jaundice may be explained on the basis of an ascending suppurative cholangitis resulting probably from further growth of the tumor nodule leading to partial obstruction immediately proximal to the site of perforation.

March 9, 1925.

BEHAVIOR OF LEUKOCYTES AND ENDOTHELIUM IN TISSUE CULTURES

ALEXANDER A. MAXIMOW
University of Chicago

Some twenty-three years ago I published a series of papers about the histology of the inflammatory process. I showed that on the field of inflammation three cell types could always be distinguished. The first are the common granular special leukocytes, emigrating out of the blood vessels and soon degenerating. The second are the fibroblasts, the local common connective tissue cells; under the influence of the inflammatory stimulus they proliferate, produce new connective tissue and finally elaborate the collagen of the scar. The third cell type are mononuclear, ameboid and phagocytic wandering cells, the macrophages of Metchnikoff. I called them polyblasts because they dis-

play a remarkable amount of prospective potencies and give rise to a multitude of various elements—giant cells, epithelioid cells, plasma cells, etc. When the acute phase of the inflammation subsides, the polyblasts remain between the fibroblasts of the scar tissue as the so-called resting polyblasts, which morphologically are identical with the resting wandering cells or clasmatocytes of the normal loose connective tissue. As regards the origin of the polyblasts, I drew the conclusion that they have a double origin; namely from mobilized, local, resting wandering cells, or clasmatocytes, and from emigrated hematogenous nongranulated leukocytes—the lymphocytes and monocytes, through rapid hypertrophy. This latter conclusion is of primary importance, as it involves one of the chief functions of the blood leukocytes, the defense reaction.

The idea of the origin of the polyblasts from emigrated lymphocytes and monocytes never became popular. For unaccountable reasons the vast majority of investigators, especially in Germany and in this country, showed a peculiar aversion to the admission of the possibility of a progressive development of emigrated leukocytes. Instead, the common endothelium of blood vessels is usually held responsible for the production of ameboid phagocytic cells in inflammation, of giant cells, epithelioid cells and even myelocytes and erythroblasts. The endothelium is believed to be endowed with an omnipotent histogenetic capacity, whereas the nongranulated blood leukocytes are in this respect completely passive elements.

It seemed to me that the method of tissue culture might be successfully applied to the solution of these problems. In vitro, the prospective potencies of various elements can manifest themselves without any restricting influences. In fact, in 1914, two Russians, Awrorow and Timofejewsky, have already succeeded in cultivating the leukocytes of human leukemic blood and in observing their transformation not only into polyblasts, but even into fibroblasts. Carrel, in 1922, has shown the same for the leukocytes of the chick.

I explanted leukocytes of the blood of the rabbit. For testing the potencies of common endothelium, I

explanted small fragments of the pia mater with its blood vessels. For comparison I explanted fragments of the liver, where the blood vessels are lined not with common endothelium, but with histiocytes, the so-called cells of Kupffer, corresponding to the resting wandering cells of the common connective tissue.

Leukocytes of the blood of the rabbit, when explanted, behave in the same way as in inflamed tissue after emigration out of the blood vessels. The granulocytes gradually degenerate, whereas the lymphocytes and the monocytes remain alive and show progressive development. The monocytes at once begin to hypertrophy and transform themselves into large ameboid and phagocytic elements, the polyblasts or macrophages; their protoplasm contains fat droplets and engulfed material. The lymphocytes also gradually hypertrophy and sooner or later join the monocytes in their transformation into polyblasts. After four or five days, the polyblasts excessively hypertrophy, become transformed into large epithelioid cells, and proliferate mitotically. If the medium contains lithium carmine, they store the dye in granular form. In cultures of blood leukocytes inoculated with tubercle bacilli the lymphocytes and monocytes assemble into clusters around the bacilli and both become transformed into large epithelioid cells, phagocytizing bacilli.

The true endothelium, for instance, in the blood vessels of the pia mater, behaves in vitro in a very typical way. From the severed end of a vessel a mass of long, slender, fusiform, proliferating cells grows; they never produce wandering cells, but very soon join the fibroblasts in their further development and cannot then be distinguished from them.

The cells of Kupffer, lining the capillaries in the liver, when explanted, are mobilized and appear as large ameboid phagocytizing, and carmine storing macrophages. This cannot, however, be considered as a proof of the capacity of endothelium to produce wandering cells; it merely demonstrates that the cells of Kupffer are not true endothelium, but histiocytes.

April 13, 1925.

EXPERIMENTAL STUDIES ON THE NATURE OF ANTIGEN AND ANTIBODY IN COMPLEMENT FIXATION IN TUBERCULOSIS

MAX PINNER

1. Evidence is presented that the alcohol soluble, acetone-insoluble fraction of tubercle bacilli contains the substances which are exclusively or chiefly antigenic in complement fixation with tuberculous sera.

2. It was not possible to prove that these substances are the only active ones, but tubercle bacillus preparations which do not contain them are not suitable antigens for complement fixation.

3. The degree of dispersion plays an important rôle in the antigenic strength of lipoidal tuberculous antigens.

4. The genuine not denatured, lipoid free proteins have as yet not been prepared from tubercle bacilli. Protein substances exert a marked inhibiting influence on the complement-fixation phenomenon.

5. The assumption that chemically different antibodies bind complement with chemically different antigens could not be substantiated.

1. The complement-fixation antibodies in tuberculous sera are not destroyed by prolonged action of trypsin. Therefore, they are neither identical nor necessarily associated with the serum globulins.

2. In tuberculous sera which by simultaneous trypsin digestion and dialysis have been rendered chemically free from proteins and protein split products, complement-fixating antibodies are still demonstrable.

3. The chemical nature of these antibodies is therefore either of the character of lipoids or of proteins with the CONH linkage which are not digested by trypsin and which may be present in so minute amounts as to be not detectable by chemical means.

4. A definite decision of this question has not been possible because the ether solubility cannot be tested because the antibodies are readily destroyed by ether.

5. Lipases with a specific action on those tubercle bacilli lipoids which are highly active in complement fixation could not be demonstrated in tuberculous sera.

Complete Report will be published in the *American Review of Tuberculosis.*

April 13, 1925.

CRYSTALLINE PROTEINS OF THE URINE

LUDVIG HEKTOEN

AND

WILLIAM H. WELKER

From the John McCormick Institute for Infectious Diseases and the Laboratory of Physiological Chemistry, College of Medicine, University of Illinois, Chicago, Ill.

Six crystalline proteins have been separated by different workers from the urine up to the time of the studies presented now.

The chemical properties, as well as the crystalline structure of these proteins, were discussed. The seventh crystalline protein was isolated from the urine by the authors from a case of myeloma. This was obtained in definite crystal form and was shown to have the same precipitin reactions as that prepared by Walters at the Mayo Clinic. Its solution showed no precipitin reaction for blood proteins, confirming the conclusions of Bayne-Jones and Wilson in their study on the Walters protein to the effect that Bence-Jones protein is not a blood protein.

The eighth crystalline protein was also prepared by the authors from the urine of a patient with prostatic enlargement and grave anemia in the care of Dr. H. L. Kretschmer. The crystal form of this protein was different from any of the others previously isolated. It showed no precipitin reactions in common with the

blood proteins, with Bence-Jones protein, or with the Noel-Paton protein, the first crystalline protein isolated from the urine. It appears to be a strictly specific antigen.

May 11, 1925.

THE ISOLATION OF HEMOLYSIN BY SPECIFIC ADSORPTION

ARTHUR LOCKE

Seymour Coman Fellow in Chemistry, Kent Chemical Laboratory, the University of Chicago

AND

EDWIN F. HIRSCH

From the Pathological Laboratory of St. Luke's Hospital, Chicago

Previous work with the fractionation of amboceptor serum by electrodialysis brought out the fact that this method, while fractionating the immune substance to a considerable degree, concentrated other pseudoglobulins as well. Since specific immune substances form definite and fairly stable compounds when mixed with homologous antigens, it seemed probable that combining amboceptor with homologous red cells and then accomplishing a cleavage would yield the most highly purified hemolysin. Liebermann and Fennyvessy in 1908 reported amboceptor solutions prepared in this way, and Kosaki ten years later reported further studies and reviewed the observations recorded in the literature at that time. In substance, these solutions have been reported as being protein free, and yet possessing the specific immune properties. There is considerable uncertainty regarding the proper evaluation of these reports because the potency of the preparations obtained was invariably small and inconstant.

A good immune serum contains 5,000 hemolyzing units (amount of amboceptor in the presence of one unit of complement necessary to hemolyze in thirty minutes 0.5 cc. of a 5 per cent sheep cell suspension made up to 2 cc. volume with normal salt solution)

per cubic centimeter and approximately 10 mg. of protein nitrogen. This is about 0.002 mg. protein nitrogen per unit. The approximate limiting concentration for an unmistakable test for proteins (except as demonstrated immunologically) is from ten to 100 times this value. Accordingly, 100 units of amboceptor in native immune serum may fail to give a protein reaction by the chemical tests. When immune serum is fractionated and a comparatively pure hemolysin has been obtained, the protein concentration is so low that 400 to 4,000 units per cc. must be present in order to give a positive chemical reaction for protein. This quantity exceeds by ten times the best preparations reported to date in the literature.

Because of these limitations in the chemical methods for detecting proteins in highly dilute solutions, it became necessary to develop a method whereby the amount of nitrogen per hemolytic unit could be determined and a ratio of potency to nitrogen expressed. The conditions for the use of the method demand also that these nitrogen values be made with a relatively small volume of liquid. Briefly stated, this was accomplished by Dr. Locke and Miss Main in our laboratory with spectrophotometric adsorption readings. Standard solutions of nitrogen were Nesslerized, and in tubes of a given length readings were made of light adsorption at different wave lengths. These values were used in constructing a series of curves indicating nitrogen content. By means of this chart other readings of unknown Nesslerized solutions can be converted into nitrogen values.

The procedure given in the literature for the fractionation of amboceptor from immune serum by selective adsorption is about as follows: Washed sheep cells are mixed with immune serum usually diluted several times with salt solution. The cells removed by centrifugation are washed with salt solution and then shaken with a weakly acid or alkaline salt solution or with an isotonic sugar solution. Ether is added to hemolyze the cells and the major part of the hemoglobin is carried into the ether-salt solution interphase along with stroma material. The clarified solution is

evaporated in a desiccator to a small volume, dialyzed, and centrifugalized free from separated material. The solutions so obtained represent the furthest advance so far reported toward the preparation of pure solutions of an hemolysin.

Many repetitions of this work have always yielded solutions with little potency. The complete removal of hemoglobin is another difficulty. Certain experiments demonstrated that cell stroma is just as effective in adsorbing hemolysin as the whole cell. Also the combination of stroma and hemolysin is more readily and quantitatively flocculated and centrifugalized from suspension than the normal stroma.

Accordingly 10 to 15 per cent red cells are added to immune rabbit serum and in the presence of native complement hemolysis takes place. About 90 per cent of the amboceptor content is removed. The sediment obtained is washed four times with salt solution. This removes the liberated hemoglobin and the inert rabbit proteins, but very little hemolysin. The sediment is then extracted three times with ether, then washed with salt solution and finally with distilled water. Then the extraction with N/1000 HCL is started and large amounts of hemolysin are liberated from the stroma.

Solutions with 2,500 units per cc. and with nitrogen values as low as 0.000.02 mg. per unit have been obtained. When the acid extracting liquid is made almost neutral with dilute alkali, iso-electric flocculation occurs. Solution and reprecipitation can be repeated just as with a recrystallization process.

The substance so obtained precipitates upon half saturation with $(NH_4)_2SO_4$, is soluble in saturated sodium chloride solution, and accordingly has the characteristics of a pseudoglobulin.

Guinea-pigs sensitized with these solutions pass into anaphylactic shock when injected after ten days with normal rabbit serum.

A complete report is published in the *Journal of Infectious Diseases,* November, 1925, **37**:449-464.

May 11, 1925.

A PATHOLOGIC SUBTILIS BACILLUS FROM A TUBERCULOUS PATIENT

H. C. SWEANY
AND
MAX PINNER

From a patient with chronic and acute tuberculosis of the lungs, kidneys and spleen and with petechial hemorrhages in the skin, mucous and serous membranes, with abscesses in kidney and spleen and with acute inflammatory changes in the endocardium and pericardium and leptomeninges, a *Bacillus subtilis* was isolated by cultures of the heart's blood, the pericardial and abdominal fluids. The same organism was found microscopically in the necrotic material from the renal abscesses. This organism grew slowly in the first three or four generations and only on blood containing media. Hemolysis was marked. The later generations were in no way atypical. This *B. subtilis* was pathogenic for white rats, in which it produced multiple pulmonary abscesses. After culturing this strain for three months, its pathogenicity was lost.

The complete report, including the bibliography, is published in the *Journal of Infectious Diseases*, October, 1925, **37**:340-343.

March 9, 1925.

CONGENITAL HYPERTROPHY OF THE VERUMONTANUM AS A CAUSE OF URINARY RETENTION

WILLIAM WITTEN ROBINSON

From the Department of Pathology of Rush Medical College

Urinary retention in the young due to anatomic lesions in the posterior urethra is often undiagnosed, and in nearly all cases reported, it has first been found postmortem. According to Young,[1] Valpeau in 1932

1. Young, H. H.; Frontz, W. A., and Baldwin: Congenital Obstruction of the Posterior Urethra, J. Urology **3**: 289, 1919.

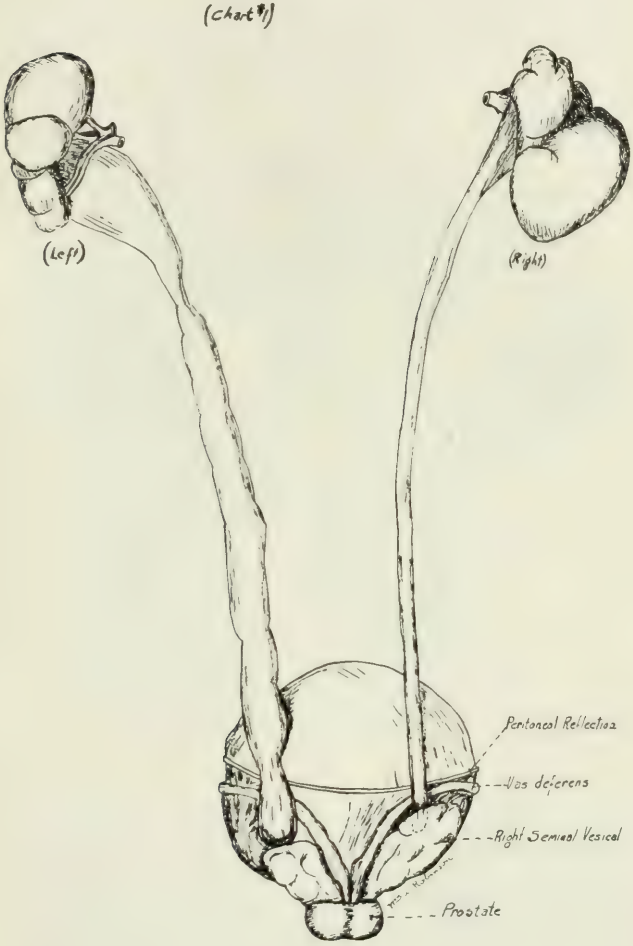

(Chart #1)
(Left)
(Right)
Peritoneal Reflection
Vas deferens
Right Seminal Vesical
Prostate

Figure 1

described folds in the posterior urethra resembling valves, and which he thought might cause urinary obstruction and Jarjavay in 1856 in a monograph concerning the male urethra also mentioned this condition. Both these writers refer to the congenital valvular obstruction of the posterior urethra noted by Langenbeck in 1802.

H. H. Young, W. A. Frontz and J. C. Baldwin [1] in 1919 reported 12 of their own and 24 cases from the literature in which chronic urinary retention, with all its

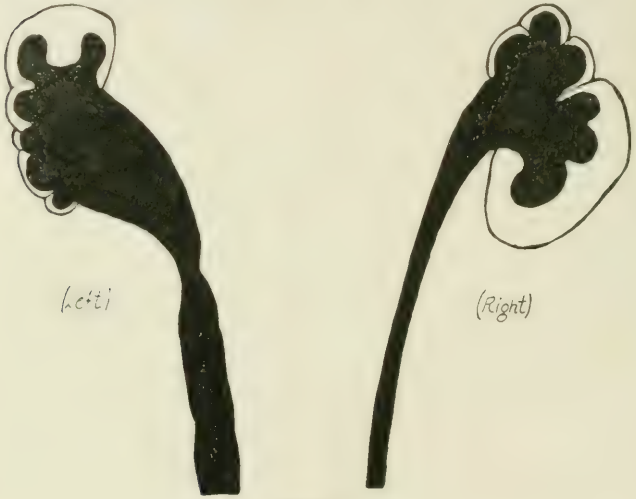


Figure 2

sequellae: hypertrophy of the bladder, hydroureter and hydronephrosis were produced by definite congenital valve-like membranes, clearly demonstrated in the posterior urethra.

No mention is made by any of these writers as to the possibility of a simple congenital hypertrophy of the verumontanum itself, without valves, as the cause of the obstruction.

When this study was begun in February, 1923, I was unable to find any reports of urinary obstruction due solely to simple congenital hypertrophy of the verumon-

tanum. Since then, H. G. Bugbee and Martha Wollstein [2] have reported six cases of double pyonephrosis, and two of double hydronephrosis with dilatation of both ureters, with in seven of the eight, an enlarged occluding verumontanum and the urethra without valves. In the eighth, there was a valve-like fold of mucosa in the urethra proximal to the verumontanum.

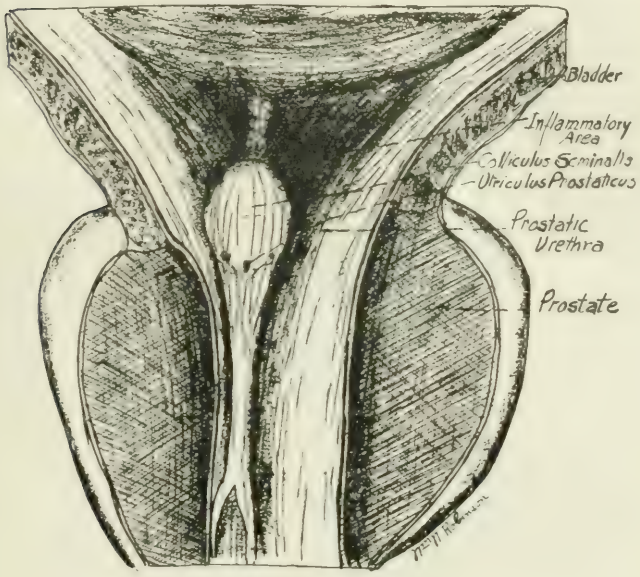


Figure 3

Case Report: The patient, age 17, was admitted to the Cook County Hospital, January 27, 1923, to the service of Dr. Ernest Irons, with acute bronchopharyngitis of three days' duration. A thorough physical examination revealed nothing except the acute respiratory infection. The blood pressure was 110 to 99 and nothing abnormal was found in the urine. He recovered quickly and at the time of his dismissal, February 2, 1923, was apparently in perfect health. Twenty-two days later he was again brought into the hospital, this

2. Bugbee, H. G., and Wollstein, M.: Retention of Urine Due to Congenital Hypertrophy of the Verumontanum, J. Urology **10**: 477 (Dec.) 1923.

time in coma, for which a tentative diagnosis of meningitis was made. So far as could be learned, this second illness had come on suddenly.

Examination at this time revealed a fairly well developed, well nourished boy of 17 years with a temperature of 101, pulse 124, noisy streptorous respiration of 36, and a systolic blood pressure of 200 mm., a diastolic of 135, and leucocyte count of 32,000. There was a slight bleeding and purulent discharge from the nose.

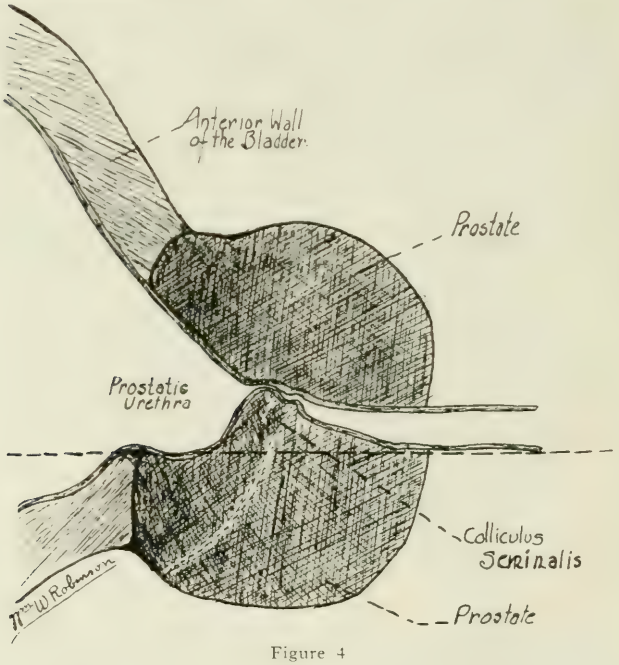


Figure 4

Pressure of the spinal fluid was not increased and in it there were only three cells per cubic mm. The Wassermann test of the blood was negative, and the blood contained non-protein nitrogen, 260.43 mg. per 100 cc., 234.88 mgs. of urea and 6.66 mgs. of creatine. Urine obtained with a catheter was "smoky," with a specific gravity of 1010, alkaline reaction, a 4 mm. ring of albumen, many red blood cells, a few pus cells but only an occasional cast and no sugar, acetone or diacetic acid. He died 25 minutes after he was taken to the ward.

Necropsy Report: (E. R. LeCount.) Except for a marked edema of the brain, the changes were confined to the urinary tract. The bladder was distended, containing 800 cc. of urine. The kidneys were markedly shrunken and atrophic, the right weighing only 45 grams, and the left kidney 20. The entire lower pole of the left kidney and the upper pole of the right were thin-walled, shrunken masses of firm, leathery tissue 1.5 mm. thick, surrounding dilated calyces. All the calyces of both kidneys were dilated and the pyramids shortened with pressure atrophy (see figs. 1 and 2).

The left ureter was uniformly dilated to a diameter of 1.2 cms., about five times the normal. The left opening of the ureter in the bladder was circular, gaping widely and about it the trigone was markedly inflamed. Dilatation of the right ureter was less than the left, and its vesical opening was only slightly gaping. The bladder wall was thick with hypertrophy, trabeculated but without sacculations or diverticula. The neck of the bladder was abruptly dilated, and so much so that the proximal portion of the verumontanum was partly inside the bladder cavity. The verumontanum was very prominent and formed a very effective plug at the bladder neck. It was very evident that increased intravesical tension had jammed the crest of the verumontanum tightly into the proximal end of the urethral canal (see figs. 3 and 4). There was no stricture distal to the verumontanum and no other irregularity in the lining or channel of the posterior urethra, nor was there any evidence of contracture of the neck of the bladder. Urine may have escaped at times when there was but slight intravesical pressure, or when such pressure was great enough to dilate the proximal part of the urethra. The conditions present readily explained why no difficulty had been encountered in catheterization.

There were moderate chronic inflammatory changes superficially in sections made at many levels in the verumontanum, chiefly a lymphocytic infiltration immediately beneath the mucosa. Glands were very abundant and about and between them relatively little fibrous stroma. There was no acute inflammation.

Discussion: The distended bladder with bilateral hydronephrosis and hydroureter, were the result of some form of chronic urinary obstruction distal to the bladder neck. That the urethra was tremendously dilated proximal to an enlarged verumontanum and normal distally, indicated an obstruction due to disparity in size of the urethra and the verumontanum, and that the verumontanum had formed an effective "ball-valve" in the prostatic urethra.

CONCLUSIONS

1. Urinary retention with the sequences, distended bladder, hydroureters, hydronephrosis, uremia and death may be produced by an obstruction in the prostatic urethra due to an enlargement of the verumontanum.

2. Since an enlarged verumontanum and congenital membranous valves produce urinary retention by means of a valve-like mechanism, patients so afflicted, may be catheterized without difficulty.

3. With large amounts of residual urine in young men and an absence of any demonstrable obstruction to the passage of a catheter, the presence in the posterior urethra of obstruction due to an enlarged verumontanum should be remembered.

The more complete article will appear in the *American Journal of Urology*.

May 11, 1925.

BIBLIOGRAPHY

Bugbee, H. G., and Wollstein, M.: Surgical Pathology of the Urinary Tracts of Infants, J. A. M. A. **83**: 1887 (Dec. 13) 1924.

Rytina, A. E.: Radical Removal of the Verumontanum with Notes on Pathology, J. A. M. A. **64**: 45, 1915.

Day, G. H.: Verumontanum and Referred Symptoms, Kentucky M. J. **14**: 143 (March) 1916.

Wolbarst, A. L.: Colliculitis or Diseases of the Verumontanum, Med. Rec. **84**: 599, 1913.

Browdy, M.: Chronic Diseases of the Verumontanum and Sexual Neurosis, Lancet **2**: 961 (Nov.) 1921.

Rosen, R.: Verumontanum and Its Relation to Hematuria, Nocturnal Emissions, and Its Treatment, J. Mich. M. S. **21**: 123 (Nov.) 1922.

Swinburne, G. W.: Diseases of the Verumontanum as a Cause of Urinary Obstruction, Am. J. Urol. **6**: 283, 1910.

GEORGE HOWITT WEAVER, M.D.

In appreciative commemoration of his faithful services as Secretary of the Chicago Pathological Society from 1894 to 1925.

TRANSACTIONS OF THE CHICAGO PATHOLOGICAL SOCIETY

VOL. XII JUNE 1, 1926 NO IV

A DIPLOCOCCUS IN MEASLES

PRESIDENTIAL ADDRESS

RUTH TUNNICLIFF

The scientific investigation of the etiology of measles began with the experiments of Dr. Hektoen in 1905. He produced the disease in man by the injection of blood drawn from patients with measles early in the disease, thus showing that the virus was present in the blood. Anderson and Goldberger later demonstrated that monkeys were susceptible to measles materials collected just before or early in the eruptive stage and that the virus passed through a Berkefeld filter. Later Nevin and Bittman found that rabbits, and Duval and D'Aunoy that guinea-pigs, reacted to the injection of measles virus. After a fairly definite incubation period depending on the method of inoculation of blood or washings from the nose and throat from patients with measles, monkeys and rabbits develop leukopenia, rise of temperature, Koplik spots and an eruption, followed by desquamation. Guinea-pigs show only a fall in the number of leukocytes, a rise of temperature and, according to Duval and D'Aunoy, a hemorrhagic nephritis. Respiratory symptoms are generally absent in the measles reaction of lower animals.

Since the aerobic blood cultures on ordinary mediums made by earlier investigators failed to demonstrate bacteria, I tried anaerobic cultures in special mediums, such as semicoagulated horse serum and ascites agar. During the preeruptive and early eruptive stage of measles, a filter passing gram-positive, green producing diplococcus was found almost constantly in the blood. It never grew in the first generation in fluid mediums, probably because they are more aerobic than solid or semisolid ones. This diplococcus was isolated in largest numbers a few hours before the appearance of the eruption. After the first generation it generally grew aerobically. The same diplococcus has been found constantly in smear preparations and cultures from the respiratory tract during the same period it was found in the blood. Specific agglutinins, opsonins and complement-fixing bodies for this coccus have been demonstrated in the blood of patients with measles as the symptoms subsided. By means of immune rabbit serum the strains of this organism from measles have been shown to belong to one biologic group. This coccus has not been found in the blood in other diseases or in normal blood.

The same symptoms and lesions produced in monkeys, rabbits and guinea-pigs by infectious measles material appeared also to be caused by this organism, because other bacteria isolated from the same plates failed to produce the measles reactions. Rabbits successfully inoculated with this measles coccus

showed no reaction when reinoculated with fresh measles material. The coccus isolated from the blood and lungs of rabbits inoculated with the measles coccus also produced a rise of temperature, Koplik spots and rashes when injected into normal rabbits.

I have also studied the skin reactions to this diplococcus with a view to obtaining light on its relation to measles. Filtrates of cultures failed to produce any reaction. The most satisfactory reaction was obtained by the intracutaneous injection of 0.2 c.c. of a twenty-four hour anaerobic ascites dextrose broth culture, killed by 0.5 per cent phenol at room temperature. Knowing that rashes could be produced in rabbits by this coccus, I first made tests in the skin of shaved rabbits. Normal rabbits reacted with circumscribed, indurated, red areas from 1 to 4 cm. in diameter within twenty-four hours after injection. Rabbits immune to measles showed no reaction to the measles antigen. Twenty-one strains of bile insoluble, green producing diplococci were then tested. The six measles strains gave marked reactions in normal rabbits, but none in rabbits immune to measles. Four strains from other sources gave reactions in rabbits both immune and not immune to measles. The other strains failed to produce any reactions.

The serum of goats and a rabbit immunized with this diplococcus, as well as convalescent human measles serum neutralized the measles antigens, but normal goat and rabbit serums failed to do so. Convalescent human measles serum did not neutralize the coccus antigens not derived from measles.

Similar tests were made in human beings with two different measles antigens. The antigen was diluted with salt solution to a point that gave no reaction in persons who had previously had measles. No reaction occurred with the control culture mediums except sometimes a redness 0.3 cm. in diameter at the site of the needle prick. Twenty-eight persons who gave a history of measles or were convalescing from measles showed no reaction. One person with a history of measles reacted positively. Twenty-six persons who had not had measles gave a definite reaction generally in twenty-four hours, in the form of a circumscribed area of erythema of varying intensity from 1 to 2 cm. in diameter, as a rule with slight infiltration. The reaction in some instances was followed by pigmentation and desquamation and generally disappeared in twenty-four hours. The serum of a person with a negative history of measles who gave a positive skin reaction failed to neutralize while convalescent human measles serum did neutralize the measles antigen when injected into persons who had not had measles.

Since these experiments suggested that this diplococcus might be peculiar to measles, it seemed worth while to try to produce immune serum in a large animal for preventive inoculations. Others have shown that monkeys, guinea-pigs and rabbits recovering from measles produced experimentally with measles virus are immune to reinfection. Scott and Simon also showed that the blood of rabbits infected with measles virus will protect uninoculated rabbits when later infected with measles material.

Nicolle and Conseil, Degkwitz, McNeal, Weaver and Crooks, Zingher and others have proved the protective power of convalescent measles serum against measles. Since monkeys, guinea-pigs and rabbits were found susceptible to the green producing diplococcus isolated from measles patients, it seemed possible that a goat might also react to this organism, and if so the blood drawn during convalescence might show protective power against measles. A goat

was chosen rather than a horse on account of the danger of sensitization with horse serum if used in other diseases and also on account of the common belief that goat serum is not toxic to man.

From nine to fourteen days after intravenous injection of living measles diplococci, goats showed a rise in temperature, a leukopenia and congestion of the mucous membrane of the mouth. Blood drawn during convalescence neutralized measles antigens when injected intracutaneously into rabbits, and protected ten rabbits against a subsequent injection of infective material from measles. The six rabbits receiving injections with normal goat serum or uninoculated before receiving the measles virus all showed some or all of the characteristics of measles in rabbits: a rise of temperature, Koplik spots and an eruption.

On account of the difficulty of always obtaining convalescent human measles serum and the indication that immune goat serum protected rabbits against measles, Dr. Hoyne and I have tried immune goat serum in a few children who had not had measles, convalescent human serum collected by Dr. T. T. Crooks being used as a control.

Of the sixteen children with a negative history of measles receiving goat serum on the first two days after exposure, twelve showed no signs of measles. Six children receiving the serum on the third day or later, developed measles. In the cases in which human convalescent measles serum was used as a control the percentages of persons who contracted measles was the same as in those receiving injections with goat serum. A number of other children also received goat serum but were later found not to have been exposed to measles.

The serum of one goat was toxic to fifteen of the twenty-three children receiving injections. It is possible that if the serum was concentrated and preserved for a longer time before using, some of the toxic effect might be avoided.

While too few experiments have been made to draw any conclusions as to the protective value of immune goat serum, we think they warrant further investigation, especially with serum of goats more highly immunized.

The coccus in pairs and short chains observed by Babes in 1880 in the secretions from the nose, conjunctiva and bronchi of patients who had measles, the diplostreptococcus isolated from the sputum by Menschikow, the gram-positive coccoid bodies seen by Mallory and Medlar in the skin and the green coccus isolated by Donges from the blood in measles may be the same coccus which I have cultivated. It is interesting that Menschikow suggested that his coccus might have the same relation to measles that the hemolytic streptococcus had to scarlet fever. The filter-passing diplococcus recently isolated by Caronia from measles differs from my organism in being gram-negative and always anaerobic. The ascites tissue medium used by him is unfavorable for the growth of my diplococcus, and after several generations they become almost invisible, and many become gram-negative. Caronia isolated the coccus he describes not only from measles material, but also from the blood of rabbits inoculated with blood from patients with measles. Selma Meyer, who worked with Caronia and studied his technic, reports that bodies like those described by him as the cause of measles and scarlet fever were found by her also in uninoculated culture mediums and in blood cultures from chickenpox, chorea, polyarthritis and other diseases, as well as from normal blood. Rabbits receiving injections with uninoculated culture medium showed bodies in the liver and

spleen like those in rabbits receiving injections with blood from patients who had scarlet fever and measles.

At the height of the attack of measles, gram-positive bacilli and other organisms were sometimes isolated from the blood, but as I did not find them in the preeruptive stage, when the blood is known to be infective, and as no opsonins, agglutinins or complement-fixing bodies could be demonstrated for them, they were not considered to be of any etiologic significance. Some of these bacilli may be the same as those isolated by Sellards and Bigelow from the blood of patients with measles, and by Kusama, Yokoyma and Ito from the kidneys of monkeys infected with blood from patients with measles.

From the experiments with the organism I isolated from measles, we find that it is constantly present in measles during the infective period and is not found in other diseases; that specific immune bodies for this coccus are in the blood of patients recovering from measles, and by means of immune rabbit serum these cocci are shown to belong to one biologic group; it produces the same reactions in lower animals as are caused by measles virus; it is isolated from rabbits so infected and the recovered coccus again produces the measles reactions in normal rabbits; animals recovering from the infection produced by this coccus are immune to infection with fresh measles materials; antigens of this organism cause a specific skin reaction in persons with a negative history of measles, and the serum of goats immunized with this coccus [1] appears to protect rabbits and human beings against measles.

October 12, 1925.

COMPRESSION MYELITIS SECONDARY TO ECHINOCOCCUS DISEASE OF VERTEBRAE AND KIDNEY

LAURENCE E. HINES

Echinococcus disease of the vetebrae is an extremely unusual cause of transverse myelitis. The rarity of the condition is emphasized by Williamson,[1] who, in 1911, was able to cite from the literature only twenty-four cases. Since 1911 there have been additional cases reported by Magath,[2] Guleke,[3] Davis and Balboni[4] and Fournier.[5]

According to a recent review by Kretchmer,[6] echinococcus disease of the kidney is also rare, and this report is based on the postmortem findings of echinococcus disease in both vertebrae and kidney.

---

1. The bibliography is given in an article entitled "Further Studies on a Diplococcus in Measles," J. Infect. Dis. **37**:193, 1925.

1. Williamson, R. T.: Diseases of Spinal Cord, London, Oxford Press, 1911.

2. Magath, T. B.: Med. Clin. North America **34**:549, 1921.

3. Guleke, A.: Deutsch. Ztschr. f. Chir. **162**:59, 1921.

4. Davis, L., and Balboni, G. M.: Boston M. & S. J. **176**:726, 1917.

5. Fournier, J. C. M.: Rev. de med. del Uruguay **21**:523, 1918; abstr., J. A. M. A. **71**:203, 1918.

6. Kretschmer, H. L.: Surg., Gynec. & Obst. **36**:196, 1923.

REPORT OF A CASE

History.—A white woman, aged 38, a native of Ireland, was admitted to St. Joseph's Hospital, Chicago, Aug. 10, 1924, complaining of paralysis and severe pain of both lower extremities, marked constipation and polyuria. The illness started about June 1, 1924, with shooting pains in the right leg. This was followed by numbness and progressive weakness in both legs.

Examination.—The examination on admittance revealed a well nourished woman, acutely ill, with a temperature of 100.2 F. and a pulse rate of 126. The essential physical findings were: distention of the abdomen, bilateral flaccid paralysis of both lower extremities; loss of thermal, tactile and pressure sensation of both lower extremities and trunk below the twelfth dorsal segment; absent patellar, Achilles and abdominal reflexes. No pathologic reflexes were obtained. Blood culture and Wassermann tests of blood serum were negative. There were 19,100 leukocytes per cubic millimeter and 81 per cent of polymorphonuclears. Urinalysis was negative on admission, but showed a trace of albumin and numerous pus cells the day before she died. Roentgenograms of the spine, spinal fluid examination and echinococcus complement-fixation tests were not made. Two days after admission she was unable to urinate or defecate voluntarily. A large sacral bed sore developed on the fourth day. The patient became very toxic, and died eleven days after admission.

Necropsy.—The anatomic findings at necropsy, made four hours after death, were: compression myelitis of the lower dorsal and upper lumbar cord; localized echinococcic pachymeningitis externa of the cord; multiple echinococcus cysts of the eleventh and twelfth dorsal and first lumbar vertebrae; large sterile (?) echinococcus cyst of the right kidney; sacral decubitus ulcer; cloudy swelling of the liver, myocardium and kidneys; chronic passive congestion of the spleen; passive hyperemia of the lungs; distended and trabeculated urinary bladder; old surgical ablation of the gallbladder; fibromyoma of the uterus; simple cyst of the left ovary and pelvic adhesions.

A large cyst, 12 by 9 by 9.5 cm., protruded from the anterior surface of the lower pole of the right kidney. One surface was partially embedded in the cortex of the kidney; the lower border was about 5 cm. below the lower pole. The cyst contained about 200 cc. of slightly turbid brown fluid. The walls were 4 mm. thick and lamellated. The lining of the cyst cavity was generally smooth, except for a few brown, granular areas and small domelike projections. No hooklets or scolices were found in the fluid content, in the smears from the lining or in microscopic sections from the wall. The bodies of the eleventh and twelfth dorsal and first lumbar vertebrae were so friable that they could be broken easily. This was due to marked sponginess or cystic changes in the bone. In the loose tissue between the dura mater of the cord and the affected vertebral bodies, a light yellow exudate was expressed, which contained a few small gelatinous cysts. Smears revealed occasional scolices and numerous hooklets. Sectioned surfaces of the cord were grossly unchanged.

COMMENT

The comparatively large size of the kidney cyst and absence of daughter cysts in the contents indicate that the kidney was infected for a long time and was probably the primary site of infection. The small

cysts in the vertebrae and around the cord suggest recent involvement, and this coincides with the short period of clinical evidence of cord compression.

Development of cysts outside the dura mater is the usual method of spinal compression. Williamson points out that it is exceptional to find cysts within the dura mater.

Any part of the cord may be involved. In Williamson's twenty-four cases, the cervical cord was involved in 2; the dorsal in 10; the lumbar in 6; the cauda equina in 5; and the dorsal, lumbar and cauda equina in 1. In this same series the site of origin was: cancellous tissue of vertebrae, 7; extradural areolar tissue, 4; arachnoid tissue, 2; muscles of back, 4; lung, 2; retroperitoneal tissue, 2.

SUMMARY

A case of echinococcus disease is reported in which the spinal cord was compressed by hydatid cysts that developed outside the dura mater. Recent cystic changes in the vertebrae and an old echinococcus cyst of the kidney were associated findings.

October 12, 1925.

FURTHER OBSERVATION ON THE RING PRECIPITATION TEST FOR SYPHILIS

RUSSELL D. HERROLD

The results of further comparative tests with the Wassermann reaction support the view that the ring precipitation test is valuable in detecting syphilis serologically.

October 12, 1925.

SOME OBSERVATIONS ON THE RELATION OF CHEMICAL CONSTITUTION TO BIOLOGIC SPECIFICITY

JULIAN H. LEWIS
AND
H. GIDEON WELLS

The cereals — emmer, *Triticum dicoccum;* durum, *Triticum durum;* spelt, *Triticum spelta;* einkorn, *Triticum monococcum* — are genetically related to wheat, *Triticum vulgare.* That einkorn has seven chromosomes, emmer and durum fourteen and wheat and spelt twenty-one, indicates the evolution of these plants by polymerization, and that the fertility or total or partial sterility of interspecies is in accordance with this idea. In like manner, kafir, *Andro-*

pogon sorghum, teosinte, *Euchlaena mexicana Schrad.* and corn, *zea mays*, are botanically related. All these plants yield alcohol-soluble proteins, or prolamines, which have been studied by Gortner and Hoffmann,[1] and which have been found to have marked chemical and physical similarities between those of the wheat group and those of the corn group. Because of these interesting genetic relationships and the chemical and physical similarities and differences between the various members of these two groups, their immunologic relationships are of particular significance and offer an opportunity for further observations on the relation of chemical constitution to biologic specificity. For this purpose the complement-fixation test was used as well as anaphylactic sensitization, determinated by three different methods, i. e., the uterus strip method, the bronchospasm method of Koessler and Lewis, and the usual anaphylactic reaction with guinea-pigs.

For the complement-fixation test, three antiserums were prepared: antigliadin (against the prolamine from wheat), antizein (aganist the prolamine from corn) and antiglutenin (against a non-alcohol-soluble protein from wheat). These antiserums were tested against 1 mg., 0.1 mg., and 0.01 mg. of all the prolamines and glutenin. The results show that the optimal amount of antigen for differentiation is 0.01 mg., and that when this amount is used the prolamines can be separated into a wheat group consisting of gliadin, emmer, durum, spelt and einkorn, and a corn group consisting of zein, teosinte and kafirin. Glutenin appears to be distinct from gliadin, although both are obtained from wheat.

Experiments with the uterus strip method confirmed the results obtained with the complement-fixation test. A uterus from a guinea-pig sensitized with a prolamine from the wheat group reacted with any other prolamine from this group but did not react with the prolamines from the corn group. After a uterus strip had reacted to a protein other than the one with which it had been sensitized, it was completely desensitized to the homologous protein.

The bronchospasm method, which shows graphically the characteristic bronchospasm of anaphylaxis, showed that zein and gliadin do not interact while zein and teosinte do. It also showed that gliadin and glutenin have no antigenic properties in common.

With the anaphylactic reactions it was found that guinea-pigs sensitized with gliadin gave strong reactions when reinjected with the other four proteins of the wheat series, but none with the proteins from the corn series. Animals recovering from these crossed reactions were found to be protected to gliadin just as were the tissues in the uterine strip experiments. Guinea-pigs sensitized with either zein or teosinte and desensitized with a heterologous protein of the same group failed, forty-eight hours later, to react with either the homologous or heterologous protein, indicating that the proteins of this group are similar enough to one another to desensitized animals.

Immunologic study of the alcohol-soluble proteins from certain cereal grains indicate that they fall into two classes. Gliadin from wheat and the prolamines from durum, einkorn, emmer and spelt, of the genus *Triticum*, seem to be closely related, according to tests by means of both the complement-

1. Gortner and Hoffmann: Second Colloid Symposium, Monographs, Chemical Catalogue Co., New York, 1925.

fixation and the anaphylactic reaction (tested by three methods). The alcohol-soluble proteins from common maize, from kafir corn and from teosinte were found to be closely related to one another, but not to the alcohol-soluble proteins of the *Triticum* group. These results agree with the observations made by others (Gortner and Hoffmann) that the chemical properties of these alcohol-soluble proteins indicate the existence of a "wheat group" and a "corn group" of prolamines, the members of each group being chemically similar to each other, as we have found them to be immunologically.

The complete report is published in the Jour. Biol. Chem. **66**:37, 1925.

November 9, 1925.

THE SPLANCHNOPERIPHERAL LEUKOCYTE BALANCE

W. F. PETERSEN

The normal level of blood pressure is maintained by an antagonistic orientation of splanchnic and peripheral autonomic impulses. In a similar manner it seems probable that the quantity of leukocytes present at any one time in any particular part of the vascular bed is controlled by a similar antagonism of autonomic impulses. Müller has previously discussed some of the underlying experiments that support this view.

Together with Müller and von Oettingen, we have studied the effect of peripheral stimulation (exposure of abdominal skin of the dog to quartz light) on lymph constituents. It has been found that irradiation is followed by immediate effects apparent in the lymph. These may be predominantly sympathetic in character (increased lymph sugar, lowered lymph protein, diminished calcium) or parasympathetic (decreased lymph sugar, increased protein and calcium). With splanchnic sympathetic orientation there is peripheral leukocytosis; with splanchnic parasympathetic orientation, a peripheral leukopenia. The usual picture is that of a wavelike change with fluctuations between the two extremes. Occasionally the waves are of increasing amplitude.

In a second group of animals, eye pressure was made with thoracic incanulation. In all instances the heart rate was slowed to approximately 50 per cent of the normal rate, parasympathetic stimulation. The lymph effect that followed might be either sympathetic or parasympathetic. Usually there were marked fluctuations between the extremes. The peripheral leukocyte count again indicated an antagonistic state from that obtaining in the splanchnic area. The possible mechanism by which the rapid fluctuation of the leukocytic curve takes place was discussed.

DISCUSSION

Dr. E. R. LeCount: Are these variations of the sugar and calcium associated with a constancy in the osmotic pressure of the lymph? This inquiry is made because I understand that the osmotic pressure of the blood is maintained at a rather constant level, but I do not know that a similar condition obtains with the lymph.

Dr. Petersen: No osmotic pressure measurements have been made, but in certain experiments the electrical conductivity has not changed, and probably there are no changes in osmotic pressure.

November 9, 1925.

GAUCHER'S DISEASE AND LIPOID HISTIOCYTOSIS

WILLIAM BLOOM

Dr. Bloom gave a demonstration of specimens and lantern slides from two cases of Gaucher's disease and three cases of lipoid histiocytosis of the Niemann type, stressing the differences between the two conditions. The complete paper is published in the *American Journal of Pathology* **1**:595, 1925.

DISCUSSION

Dr. R. H. Jaffé: The histology of Niemann's disease resembles somewhat the lipoid changes found in the internal organs of children dying of malnutrition. The epithelial reticulum cells of the thymus, especially, are enlarged and are filled with lipoid droplets. There are differences as regards the extension of the process and the microchemical reactions of the deposited fat substances, but these may be merely quantitative, the fundamental cause being the same, namely: a severe disturbance of the lipin metabolism. Since the microchemical tests are not reliable, a chemical analysis of the organs in Niemann's disease and malnutrition would be valuable. Chemical studies of the spleen in morbus Gaucher have yielded interesting results.

November 9, 1925.

ANEURYSM AND ANOMALY OF THE CIRCLE OF WILLIS*

LAWRENCE JACQUES

True aneurysms of the cerebral arteries are to be sharply distinguished from the so-called miliary aneurysms of the brain. The latter are said to be demonstrable by maceration methods in almost every case of cerebral apoplexy occurring after 40 (Osler).[1] They are usually about as large as a pinhead, involve the finer vessels within the brain, and frequently (Pick)[2] are simply minute hematomas representing

---

* From the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research.

1. Osler, W.: The Principles and Practice of Medicine, New York, D. Appleton & Co., 1912.

2. Pick, L.: Ueber die sogenannten miliaren Aneurysmen der Hirngefässe, Berl. klin. Wchnschr. **47**:325 and 382, 1910.

hemorrhages which have occurred from direct rupture of the vessel wall. The former, on the other hand, are less common, having been encountered in from 0.2 to 1.5 per cent. of various series of necropsies (Pitt,[3] Osler, Reinhardt,[4] Fearnsides[5]). Three have been encountered in 1,308 necropsies performed at the Michael Reese Hospital since 1909. They may occur at almost any age, involve as a rule the large vessels at the base of the brain, occasionally those of the convexity, and are usually the size of a pea or a cherry pit, becoming in some instances as large as a walnut or even a small orange.

True cerebral aneurysms are of pathologic interest chiefly because of the difficulties frequently involved in establishing their etiology. Because of these difficulties, many of the aneurysms of obscure etiology reported in the literature, particularly those occurring in persons in the earlier decades of life, have been attributed by exclusion to hypothetical congenital hypoplastic defects in the vessel walls. Attention has been called, however, to the frequency of gross developmental anomalies of the vessels at the base of the brain by the anatomic studies of Windle,[6] Parnisseti,[7] Wyrubow[8] and DeVries.[9] The possible causal relationship of such deviations to the formation of aneurysms of the basilar artery was first suggested by Lebert.[10] The point was later reiterated by von Hofmann,[11] with respect to the vessels at the base of the brain in general, with the statement: "It is not impossible that many of these anomalies can contribute to the formation of aneurysms through an uneven division of blood volume and pressure." Individual instances involving such an association have been described by Ebstein,[12] Weir

3. Pitt, W.: On Cerebral Embolism and Aneurysm, Brit. M. J. **1**:827, 1890.

4. Reinhardt, A.: Ueber Hirnaneurysmen und ihre Folgen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:432, 1913.

5. Fearnsides, E. G.: Intracranial Aneurysms, Brain **39**:224, 1916.

6. Windle, B. C. A.: On the Arteries Forming the Circle of Willis, J. Anat. & Physiol. **22**:289, 1888.

7. Parnisseti, C., quoted by Rothman, M.: Ueber das Verhalten der Arteria cerebri anterior beim Affen, Anthropoiden und Menschen, Arch. f. Psychiat. **38**: 285, 1904.

8. Wyrubow, quoted by Rothman.

9. DeVries, B.: Sur la signification morphologique des artères cérébrales. Arch. de biol. **21**:357, 1905.

10. Lebert, H.: Ueber Aneurysmen der Gehirnarterien, Berl. klin. Wchnschr. **3**:209, 229, 249, 281, 336, 345, 387, 402, 1866.

11. Von Hofmann, E. V.: Ueber Aneurysmen der Basilarterien und dessen Ruptur als Ursache des plötzlichen Todes, Wien. klin. Wchnschr. **7**:823, 1924.

12. Ebstein, W.: Aneurysma einer unpaaren Arteria cerebri anterior, Deutsch. Arch. f. klin. Med. **12**:617, 1874.

Mitchell [13] and Berger.[14] More recently Busse,[15] noting the preponderance, in his experience, of aneurysms involving the anterior communicating artery, was led to make a careful anatomic study of this region. He found deviations from the normal in 227 of 400 brains examined, ranging from simple doubling of the vessel to the most intricate and fanciful plexus formation. These abnormalities were regarded by him as evidences of arrested embryologic development. In thirty-nine cases, almost 10 per cent., dilatation of some anomalous vessel in such a group had occurred, with the formation of a true aneurysm. Microscopically, the walls of such outpouchings were found to be thinned, the elastica interna stretched and sometimes broken; but no other evidences of disease or degeneration were to be made out. The possible formation of these aneurysms on the basis of purely mechanical factors was suggested, and the opinion ventured that a careful study of other portions of the circle of Willis might disclose a similar condition.

Attention is called by Merkel [16] in Henle's "Grundriss der Anatomie" to the occurrence of anomalies of the posterior communicating arteries, the vessels involved in the case to be reported. Windle, in his study of 200 brains, encountered forty-three cases in which there was a marked disparity in the size of these vessels, nine in which the right was absent, thirteen with absence of the left, and three in which both were absent. Mitchell was able to collect from the literature sixteen anomalies of the posterior communicating arteries. In nine of these, the vessels were absent or impervious. DeVries quotes references to forty-five anomalies of the posterior communicating arteries, in seven of which both vessels were absent. In no case in any of these series had aneurysms occurred. Indeed, except for two of the cases reported by Berger, no instances of association of aneurysms and anomalies of these vessels have been found. It is felt, therefore, that the coincidence of these conditions is of sufficient interest to justify the following report.

REPORT OF A CASE

History.—Mrs. C. T., aged 72, housewife, was first admitted to the Michael Reese Hospital, to the medical service of Dr. Solomon Strouse, on April 4, 1923.

---

13. Mitchell, S. W.: Aneurysm of an Anomalous Artery Causing Antero-Posterior Division of the Chiasm of the Optic Nerves and Producing Bitemporal Hemianopsia, J. Nerv. & Ment. Dis. **14**:44, 1889.

14. Berger, W.: Ueber Aneurysmen der Hirnarterien, Virchows Arch. f. path. Anat. **245**:138, 1923.

15. Busse, O.: Aneurysmen und Bildungsfehler der Arteria communicans anterior, Virchows Arch. f. path. Anat. **229**:178, 1921.

16. Merkel, F.: Henle's Grundriss der Anatomie des Menchen, Braunschweig, F. Vieweg und Sohn, 1901.

Her father died at the age of 64 "of an aneurysm." Her husband died at the age of 60 of heart trouble. She had been married for twenty-one years, but had never been pregnant. At 40 she had an attack of pleurisy. Five years later, she had had typhoid fever, and several times during the last few years some of the joints of her limbs had become stiff and swollen. Eighteen months previous to admission she had had erysipelas of the face, which subsided in about ten days. During the last two years, she had slowly lost weight and strength and was bedridden most of the time. There were occasional brief attacks of weakness and dizziness, and she had noticed that her vision was gradually becoming impaired.

Examination.—The patient was poorly nourished and restless. The blood pressure was 110 systolic and 60 diastolic. There was no cardiac enlargement. A short harsh systolic murmur was heard over the apex and was transmitted to the vessels of the neck. The pupils were round and equal, but responded sluggishly to light and during accommodation. The knee and Achilles reflexes were very active. There was no ankle clonus. The biceps and triceps reflexes were present. The Babinski sign was negative.

The following ophthalmoscopic findings were recorded: Right eye: typical retinal sclerosis with moderately tortuous vessels and punctate areas of exudate. The disk was fairly normal. Left eye: retinal sclerosis of much higher degree, with larger and more numerous areas of exudate, one of which involved the macula. Fairly advanced atrophy of the optic nerve, "probably due to the retinal atrophy."

Urine: The twenty-four hour output was 26 ounces. The specific gravity was 1.018. There was no albumin. There were occasional hyaline and granular casts.

Course of Illness.—Her course in the hospital was uneventful, except for occasional "rheumatic" muscular pains and a brief unexplained fever. She was discharged unimproved.

Second Admission.—On March 2, 1925, more than two years later, she returned. In the interval her weakness and dimness of vision had been progressive, and during the few months preceding entrance she developed a severe mental disturbance which necessitated her being confined to a sanatorium. While in a period of excitement, on the day before her final admission to the hospital she jumped from a second story window, and sustained a fracture of the left humerus. On entrance to the hospital she was completely disoriented and had hallucinations, so that restraint was required. On March 27, the temperature rose to 102 F.; evidences of consolidation appeared over both bases, and she became comatose. A flaccid paralysis of the right arm was noted, and a final diagnosis of bronchopneumonia and possible cerebral thrombosis was made. On March 29, 1925, she died.

Necropsy.—There was bilateral pneumonia of the hypostatic type.

The heart was not enlarged. On the cusps of the aortic and mitral valves there were rows of small, firm, beadlike vegetations. The leaflets themselves were thickened and shortened as were the papillary muscles. The myocardium was of good consistency; its cut surfaces showed a moderate amount of grayish-white streaking. Microscopically, the vegetations consisted of dense fibrin and a few round cells. The valves were diffusely scarred and hyalinized and in places showed evidences of atheromatous change. About many of the small vessels in the myocardium were collections of large mononucleated and multinucleated cells

with relatively large nuclei and slightly purple cytoplasm, similar to the cells described by Aschoff as characteristic of rheumatic fever.

The kidneys presented the picture of a moderately advanced chronic diffuse nephritis. Microscopically, occasional small hyaline thrombi were found in the glomeruli.

1 indicates the anterior cerebral arteries; *2*, anterior communicating artery; *3*, middle cerebral arteries; *4*, opening of aneurysm into the left carotid artery; *5*, right internal carotid artery; *6*, aneurysm; *7*, right posterior communicating artery; *8*, right posterior cerebral artery; *9*, basilar artery; *10*, vertebral arteries; *O. R.*, right optic nerve; *O. L.*, left optic nerve.

In the aorta there was an intense sclerosis of the senile type. The splenic artery was long and tortuous, with marked yellowish intimal streaking.

The findings of chief importance, however, related to the examination of the head. The pachymeninges were thickened and in places firmly adherent to the

calvarium. The brain was symmetrical. The leptomeninges were diffusely thickened and whitened.

The vessels at the base of the brain were rather narrow, and in their walls were many sclerotic plaques. The vessel arising from the right internal carotid artery at the usual point of origin of the right posterior communicating artery was large and passed posteriorly between the cerebellum and the occipital lobe in the course normally taken by the posterior cerebral artery. The left posterior communicating artery was absent. The left internal carotid artery, just after its emergence from the cavernous sinus, was dilated to a diameter of 1.2 cm., and extending medially from it was a rounded aneurysmal sac measuring 2.5 by 2 by 1.5 cm. Over the superior and anterior surfaces and proceeding to the basal aspect of this sac, were spread the fibers of the optic chiasm. From the basal surface to which they had been adherent, emerged the flattened optic nerves. The left optic nerve had been reduced to a narrow compressed band. The right was less involved. The lumen of the sac was almost completely filled with a red and white thrombus. That portion of the wall of the aneurysm adjacent to the skull was composed of thin, fairly tough, white tissue. When the sac was dissected away from the brain, however, its wall on this side was found to be extremely thin and blood stained; the enclosed thrombus almost protruded through it. The contiguous brain substance was also stained with blood. There was a superficial erosion of the sphenoid bone where the aneurysm had rested on it.

The vertebral arteries were about equal in size. The left posterior cerebral artery emerged from the basilar. The right posterior cerebral artery was absent.

Microscopic Examination.—Microscopically, the leptomeninges were considerably thickened and sprinkled with round cells and large mononuclear phagocytes containing iron pigment. The meningeal vessels appeared normal, and there was no infiltration of round cells about them. The posterior wall of the aneurysm was reduced to a thin layer of hyalinized fibrous tissue which was fused with the enclosed thrombus and covered by an adherent layer of compressed brain tissue in which were scattered many large cells laden with iron pigment. It was sprinkled with many leukocytes and red blood corpuscles, and no muscle or elastic fibers could be demonstrated by the van Gieson and Verhoef stains.

A similarly stained section through the wall of the sac near its origin was composed of dense hyalinizing fibrous tissue, some young fibroblasts, and a few very fine, irregular, black elastic fibrils.

COMMENT

Berger's analysis may be applied briefly to the mechanical factors which may have been involved in this case. The pulsations of the heart are transmitted with particular intensity to the left internal carotid artery because of the direct origin of the common carotid on this side from the aorta. Particularly vulnerable to the effects of this stress is the point at which the internal carotid suddenly emerges unsupported from the cavernous sinus. Relief from this strain is normally afforded by the distribution of blood from the internal carotid into the anterior and middle cerebral and posterior communicating arteries. In the present case, however, the latter outlet was absent, and the strain was further

increased by the break in the circle on the right side resulting from the abnormal course of the right posterior communicating artery. The formation of an aneurysm as a result of these factors may have been favored further by the presence of an area of lessened resistance at the site from which the left posterior communicating artery normally should have emerged.

The rôle of the extensive atherosclerosis present in the cerebral vessels in this case is not to be disregarded. It is possible that these changes were responsible for the onset of the lesion relatively late in life, while the mechanical conditions described served at best only as predisposing factors of minor importance. Busse pointed out that most of his aneurysms occurred after 40, when some degree of sclerosis is almost always present, and in both of Berger's cases the cerebral vessels were rigid and extensively calcified. Nevertheless, the relationship of atherosclerosis to the production of these aneurysms is not clear, and its importance has been minimized by Lebert, Fearnsides and Reinhardt. Certainly it is true that the most intense degree of sclerosis may confer no apparent tendency to aneurysm formation, while frequently, in cases which have been attributed by exclusion to such changes, arterial degeneration of only mild degree has been present.

Syphilis is a less frequent cause of these lesions than atherosclerosis (Kaufmann [17]) and is held responsible for a relatively small proportion of the cases in the literature. No evidences of this disease were present clinically or anatomically in the present case.

The cardiac lesions encountered were undoubtedly of rheumatic origin. Those aneurysms which have been attributed to mycotic embolism of the cerebral vessels have been associated with the bacterial endocarditides. However, a few cases have been recorded by von Jaksch [18] and by Löwy,[19] in which cerebral aneurysms have been accompanied by evidences of a healed or active rheumatic cardiac infection. Löwy regards such aneurysms as evidences of direct arterial damage by the infective agent, and points out that Eppinger considered angina, rheumatism and scarlet fever as important factors in the pathogenesis of these lesions. It is interesting in this connection that Pappenheimer

17. Kaufmann, E.: Lehrbuch der Speziellen pathologischen Anatomie. Berlin and Leipzig, Walter De Gruyter and Co., 1922.

18. Von Jaksch, R.: Klinische Beiträge zur Kenntnis der Gehirnaneurysmen jugendlicher Individuen, Prager med. Wchnschr. **38**:483, 1913.

19. Löwy, J.: Das Hirnarterienaneurysma als Nachkrankheit des Glenkrheumatismus, Zentralbl. f. inn. Med. **43**:505, 1922.

and von Glahn [20] have described changes characteristic of rheumatic fever occurring in the aorta. The present case and those of von Jaksch and Löwy suggest the possible occurrence of similar changes involving the smaller arteries. No evidences of such involvement were found here, however, either in the aorta or in sections taken from the cerebral vessels.

Clinically there was little here on which to base a diagnosis of cerebral aneurysm. The absence of evidences of increased intracranial tension and particularly of choked disks is characteristic of these lesions (Oppenheim,[21] Beadles [22]) and may be of some diagnostic importance when accompanied by distinct focal evidences of pressure. A progressive unilateral or bilateral amaurosis as was present here is perhaps the most typical of the focal lesions produced by aneurysms in this location (Lebert). It is worthy of mention that the clinical picture may in some instances be fairly characteristic (Symonds,[23] Burchardt [24]), and that with the occurrence of one or particularly a series of apoplectiform seizures in a young person, in the presence of focal evidences of tumor, the possibility of a rupturing or ruptured cerebral aneurysm is to be considered seriously.

SUMMARY

In a woman, aged 73, the circle of Willis was bilaterally incomplete. The right posterior communicating artery took the course normally taken by the right posterior cerebral artery. At the site of origin of the left posterior communicating artery was an aneurysm 2.5 cm. in greatest diameter.

Cerebral aneurysm associated with anomalies of the posterior communicating arteries of the circle of Willis is rare. Abnormality in the distribution of the blood due to such anomalies may be a mechanical factor in the causation of cerebral aneurysms. The senile atherosclerosis present in the case reported may have had a part in the formation of the aneurysm, rendering the involved vessel more susceptible to the

---

20. Pappenheimer, A., and von Glahn, W. C.: Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Cardiac Diseases of Rheumatic Origin, J. Med. Res. **44**:489, 1924.

21. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, Berlin, S. Karger, 1913.

22. Beadles, C. F.: Aneurysms of the Larger Cerebral Arteries, Brain **30**: 285, 1907.

23. Symonds, C. P.: Contributions to the Clinical Study of Intracranial Aneurysms, Guy's Hosp. Rep. **73**:139, 1923.

24. Burchardt, H.: Die chirurgische Bedeutung der Gehirn-Aneurysmen, Burns Beitr. z. klin. Chir. **133**:429, 1925.

mechanical factors brought about by the anomalies of the circle of Willis.

The aortic and mitral valves and the myocardium were the seat of recent rheumatic changes. There was nothing to indicate that such changes occurring at an earlier period of life had a part in the formation of the aneurysm. There was no clinical or anatomic evidence of syphilis.

Progressive amaurosis, more marked on the left than on the right side, was the essential clinical manifestation of the condition.

November 9, 1925.

THE MEINICKE MICROREACTION IN SYPHILIS*

ANNYMARIE PETERSEN SAUNDERS

In recent years many attempts have been made to diagnosis syphilis by a method which would be specific in character and have a more simple working basis than the Wassermann reaction.

In 1917, Meinicke and Sachs-Georgi proposed a test for syphilis based on a white precipitation when an alcoholic extract of a normal heart was added to the blood serum of a syphilitic person. Since this was not a true precipitin test from a biologic standpoint, it has been called a floccule formation test. The early flocculation tests, however, had many disadvantages, and the procedure was not altogether simple. The length of time required was from twenty-four to forty-eight hours, and gave rise to erroneous results on account of bacterial contamination. In many cases the reading was indefinite. In the course of years most of the objectionable features have been eliminated, and Meinicke, in his third modification, using tulol balsam extract of horse heart, demonstrated that a turbidity precedes the floccule formation. This takes place within an hour and is easily recognized by the naked eye.

The nature of the floccule formation as well as the Wassermann reaction is as yet not entirely understood. Meinicke considers his test to be a true immunity reaction, depending on a specific antibody.

The ordinary Meinicke[1] test is carried out in the following manner: Two tubes, one containing 1 cc. of the Meinicke extract, the other 10 cc. of a 3 per cent sodium chloride solution, are kept in a water bath at a temperature of 45 C. for ten minutes; then extract and salt solution are mixed and used immediately for the test. One part of the patient's serum, and five parts of the freshly mixed extract dilution are measured into a small test tube, shaken and kept at room temperature protected from light for one hour. After that time the negative specimens are found unchanged, and the positive specimens have become almost opaque when held up to the window screen in daylight.

---

* From the State Psychopathic Institute.

1. Meinicke, E.: Meinicke Microtest for Syphilis in Children, Med. Klin. **21**:123-134 (Jan. 25) 1925. Dohnal: Technic of Meinicke Microreaction, Dermat. Wchnschr. **80**:367 (March 7) 1925; **80**:408 (March 14) 1925. Schükri: Meinicke's Turbidity Reaction, München. med. Wchnschr. **72**:183 (Jan. 30) 1925.

In a recent publication Meinicke describes a microreaction. In all tests for syphilis heretofore large quantities of blood serum were necessary. A microreaction has been attempted with the Wassermann and Sachs-Georgi tests, but has not been found practicable. Meinicke saw in his method which required no inactivation of the blood serum a much better chance for a microreaction.

The blood can be obtained from the ear, one drop being drawn up into a tube of 10 cm. in length and 1 to 2 mm. in width. Then one end of the tube is sealed if the examination is to be made in the same place, otherwise both ends need to be sealed. After coagulation has taken place, this tube is centrifuged and the part of the tube containing the clear serum is separated from the rest by means of a glass file and is then ready for use.

To 600 cc. of a 3 per cent solution of sodium chloride 0.1 Gm. of sodium carbonate is added. Of this solution 5 cc. are measured into one test tube and 0.5 cc. of the Meinicke extract into a second test tube. Both tubes are

Findings with Wassermann and Meinicke Tests

Wassermann Test		Meinicke Test	
Negative	799	Negative	799
Positive	111	Positive	111
Anticomp	9	Negative	9
Anticomp	13	Positive	13
Doubtful	8	Positive	8
Doubtful	7	Negative	7
Negative	13	Doubtful	13
Positive	5	Doubtful	5
Negative	19	Positive	19
Positive	16	Negative	16

put into a waterbath of 45 C. for ten minutes. The warm extract and the saline solution are mixed quickly. A cover glass preparation is now made, using one small platinum loop full of blood serum to one large platinum loop full of diluted extract. The large platinum loop must be of such a size as to hold exactly five times as much as the small loop. Serum and extract are thoroughly mixed on the cover glass, and a hanging drop preparation is made. The slide is kept in the dark at room temperature of not more than 20 C. for one hour, when the reading can be made under the microscope with a high dry lens. In negative specimens the field looks almost empty; here and there a few dancing spots are seen. In positive specimens definite clumping has taken place, giving, a picture similar to the positive Widal reaction. Instead of the platinum loops method, which may become inaccurate easily, leukocyte pipets have been used.

Meinicke recommends not to make more then ten preparations with the same extract dilution, as on long standing an opacity may be produced giving a false positive reaction.

The reading should be made at the end of one hour; a second reading may be made after another hour, but a longer delay is likely to cause unspecific changes which render the results a good deal more indefinite and even false.

Of 1,000 specimens of blood serum which were tested by both the Wassermann and the Meinicke methods, my results are as given in the table.

Of the nineteen cases that were negative with the Wassermann and positive with the Meinicke reaction, eleven had a history of syphilis or had had a positive Wassermann reaction a few years before. Eight specimens of the thirteen specimens from the tuberculosis hospital were doubtful with the Meinicke and negative with the Wassermann reaction. Of the sixteen cases with a positive Wassermann and a negative Meinicke reaction, eleven were cases of general paralysis in which the patients had received two years of intensive treatment with tryparsamide and sulpharsphenamine. This treatment had been discontinued two weeks prior to the tests.

The Meinicke test both in the macroscopic or microscopic method is especially valuable when the Wassermann test is anticomplementary or doubtful. Most of the blood serums we are handling are sent in from a distance and are several days old before reaching us. Occasionally some have become slightly anticomplementary or hemolytic. In a fairly large number of persons with syphilis of long standing, the kind that are likely to be admitted to the state hospital, a negative or doubtful Wassermann test on blood serum is not uncommon, while in many the Meinicke test is positive.

SUMMARY

The advantage of the microscopic over the macroscopic Meinicke test is the easier detection of floccules and the minute quantity of blood serum necessary. The microscopic test requires accuracy and a room temperature not above 20 C. (70 F.). In experienced hands it is a valuable adjunct in the diagnosis of syphilis.

December 14, 1925.

FAT REPLACEMENT OF THE GLYCOGEN IN THE LIVER AS A CAUSE OF DEATH*

E. R. LeCOUNT
AND
H. A. SINGER

During efforts to produce a cirrhosis of the liver in animals with alcohol, as well as during experiments designed simply to ascertain the effects of alcohol on its structure, an accumulation of the fat in the liver cells has been found so commonly as the main alteration that a relation between alcohol and fatty changes in the liver has long been recognized.

Rosenfeld [1] furnished rather conclusive evidence of this relation by withholding glycogen-forming foods from the diet of animals fed with

---

* From the Pathological Laboratories of Rush Medical College, University of Chicago, and the Cook County Hospital.

1. Rosenfeld, G.: Fettbildung, Ergeb. d. Physiol. **2**:50-94, 1903; Beiträge zur pathologie des Alkohols, Zentralbl. f. Med. **21**:1049-1060, 1900.

alcohol and observing fatty changes of the liver as a sequence. In discussions of this subject, it has long been customary to refer to the demonstration of fatty changes by Friedenwald [2] as the chief effect in rabbits from long-continued administration of alcohol.

The conclusions of Formad [3] based on postmortem examinations of the bodies of 250 chronic alcoholics, and the presence of large fatty livers in 90 per cent of these has more recently been corroborated by Fahr [4] from an examination of 309 such bodies. Fahr states definitely that a fatty liver is the most constant change with chronic alcoholism, and similar statements by others [5] are not wanting.

Although, as first stated, acceptance of this association of alcohol with marked fatty changes of the liver has in these various ways become general, no such agreement has as yet been arrived at with regard to symptoms enabling an estimate clinically of the degree to which the liver has suffered such alterations, and this notwithstanding the attention this phase of the subject has received since Louis [6] first called attention to marked fatty changes of the liver and especially its association with tuberculosis. That such hepatic disease may be encountered in the bodies of persons who are apparently well has been commented on by Frerichs [7] and Begbie,[8] and the absence of symptoms, except those connected with its increased size, has been the subject of comment by many writers [9] in considering marked fatty degeneration of the liver.

---

2. Friedenwald, J.: The Pathologic Effects of Alcohol on Rabbits, J. A. M. A. **45**:780-784, 1905.

3. Formad, H. F.: The "Pig-Backed" or Alcoholic Kidney of Drunkards, Tr. Am. Assn. Physicians **1**:225-236, 1886.

4. Fahr, T.: Zur Frage des chronischen Alkoholismus, Verhandl. d. deutsch. path. Gesellsch. **13**:163-169, 1909.

5. Moebius, E.: Die Fettleber, Deutsch. Klin. **2**:240-241, 1850. Schüppel, O.: Fettleber, Hepar Adiposum, Handl. d. Spec. Path. (Ziemssen), Leipzig **8**:389-419, 1878. Weichselbaum, A.: Discussion, Verhandl. d. deutsch. path. Gesellsch. **13**: 169, 1909. McJunkin, F. A.: The Human and Animal Liver After Alcohol, Arch. Int. Med. **19**:786-800, 1917.

6. Louis, P. C. A.: Recherches anatomiques, pathologiques, et therapeutiques sur la phthisie, trans. by Charles Cowan, Washington, D. C., 1836.

7. Frerichs, F. T.: Diseases of the Liver, trans. by Charles Murchison, New York **1**:196-219, 1879.

8. Begbie, J. W.: Fatty Liver, in Reynolds: A System of Medicine, London **3**:360-370, 1871.

9. Addison, T.: Observations on Fatty Degeneration of the Liver, Guy's Hosp. Rep. **1**:476-483, 1836. Bamberger, H.: Die Fettleber; Schmidt's Jahrb. d. ges. Med. **79**:298-300, 853. Murchison, C.: Clinical Lectures on Diseases of the Liver, New York, 1868, pp. 43-52. Rolleston, H. D.: Diseases of the Liver, Gallbladder and Bile Ducts, London, pp. 426-433, 1912.

Some authorities have emphasized the greater ease with which persons with such hepatic disease succumb to infections and infectious diseases. Gilbert and Lereboullet [10] also have pointed out this bearing, but they have gone much further and frankly challenged the laissez faire attitude of clinicians regarding the absence of distinctive symptoms, asserting that competent study should demonstrate impaired function of livers so diseased.

One of us (E. R. L.) has been greatly impressed for many years by encountering huge fatty livers at rare intervals during routine postmortem examinations; these were frequently found in the bodies of small women whose consumption of whisky or similar liquors (brandy) was inordinate. Little else was found within the bodies to explain death, which was often sudden or unexpected and not the result of delirium tremens. Two examples of such deaths follow.

Case 1.—J. C., a white woman, aged 45, entered the Cook County Hospital, in the service of Dr. Hassin, March 21, 1924, at 2:00 p. m., and died much to the surprise of those in attendance twelve hours and fifteen minutes later.

The preliminary diagnosis was neurasthenia and the assignment was "neurology." The following was written after death: "This ambulatory patient complained on entrance of vague gastric symptoms, generalized aches and pains, and occipital headache. A superficial examination revealed nothing abnormal. The pulse was strong, the temperature normal and she was resting quietly. At 9:00 p. m., when I visited her, she was apparently in good condition, and death was unexpected." After 1:30 a. m., the nurse noted groaning respirations, a weak pulse and cyanosis of the face, and these continued until death at 2:15 a. m. After death, it was learned that she had been drinking heavily, and was nervous and weak.

Anatomic Diagnosis.—The diagnosis was: marked fatty changes of the liver; moderate edema of the leptomeninges; hyperplasia of the spleen; marked passive hyperemia of the kidneys and bowel lining; sclerosis of the aorta and front mitral leaflet; submucous minute petechial hemorrhages of the pancreatic duct; varicose veins of the lower extremities; slight anasarca (ankles); acute catarrhal conjunctivitis; fibrous adhesions between the liver and diaphragm, spleen and diaphragm, and spleen and liver.

The liver weighed 2,900 Gm. and presented the well-known alterations of "large fatty liver," grossly and microscopically. Chemical examination of the abdominal viscera and of the gastric and intestinal content failed to disclose the presence of alcohol or any other poison.

Case 2.—J. D. C., a white man, aged 54, entered the Cook County Hospital in the service of Dr. Hamberger, May 24, 1924, at 9:30 p. m., with a diagnosis of chronic alcoholism and cirrhosis of the liver. He was seen by the resident physician of the ward at 10:35 p. m., and appeared to be in fairly good condition, but he died abruptly about ten minutes later. A brother said the patient had been

10. Gilbert, A., and Lereboullet, F.: La steatose latent des alcoholiques. Bull. et mém. Soc. med. d. hôp. de Paris **19**:577-585, 1902.

addicted to alcohol for many years, recently had used "moonshine," and for about a week had complained of weakness, tremor, nausea and epigastric distress.

Anatomic Diagnosis.—The diagnosis was: marked fatty changes of the liver; edema of the leptomeninges; moderately lessened "lipoid" of the suprarenal cortices; cholesterol deposits in the liver and kidneys; almost empty bowel; hypertrophy of the heart; passive hyperemia of the spleen, kidneys, liver and bowel; calcified tracheobronchial lymph glands; retention cysts of the left kidney; left focal fibrous pleuritis; fibrous localized perihepatitis; lessened colloid (atrophy) of the thyroid gland.

Chemical examination of 254 Gm. of stomach and content yielded 0.34 cc. of alcohol, but no other poison.

In the table, the age, sex, and ratio of the liver to body weight are given.[11] A much larger series could easily be tabulated by using more necropsy records, but it is believed that these few from recent necropsies answer the purpose. It is of special significance that of the eleven, five were women.

Ratio of Weight of Liver to That of Body

Patient	Age in Years	Sex	Body Weight in Kg.	Weight of Liver in Gm.	Ratio of Liver to Body Weight
M. S.	28	F	39.46	3,263	1 to 12.09
J. W.	40	M	63.14	4,148	1 to 15.91
C. G.	43	F	41.81	2,980	1 to 14.37
M. M.	43	F	51.59	3,200	1 to 16.08
J. F.	54	M	57.16	3,120	1 to 18.32
J. O.	45	F	55.68	2,900	1 to 19.86
G. K.	31	M	62.73	3,150	1 to 19.51
J. B.	31	M	60.00	2,991	1 to 20.02
J. D. O.	54	F	56.00	2,500	1 to 22.22
L. T.	41	M	53.97	3,090	1 to 17.46

About one-half hour before the death of one patient, a convulsion occurred with frothing at the mouth and cyanosis; another was subject to "fits," but had none during the three days he was in the hospital.[12]

For one of these patients, the clinical diagnosis was delirium tremens, but when death occurred this had largely cleared up; for six, the diagnosis was chronic, and for two acute, alcoholism; for two cirrhosis of the liver. The enlargement of the liver was usually noted clinically, once thought to be due to secondary growths from a rodent ulcer of the face, once regarded as hypertrophic cirrhosis. In six patients there was jaundice—marked in only one.

Some bronchopneumonia developing during the last days in the hospital, due to poor pulmonary ventilation and infection of dependent parts of the lungs, was present in a number of bodies.

In considering the way in which death is brought about in cases such as these, acute poisoning from alcohol is excluded by the absence of

11. The normal ratio of the liver to the body weight is from 1:31 to 1:36. Vierordt, H.: Daten und Tabellen für Mediziner, Ed. 3, Jena, 1906.

12. The term "whisky fits" has long been in common use by policemen.

coma, for alcohol causes death in an acute condition as does ether and similar anesthetics. Drinking of a large amount of alcohol, as occurs at times on a wager, is followed by stupor, then coma and death. Delirium tremens may also be excluded, although, as stated, one of the patients had delirium tremens shortly before death. It is of some significance that the lining of the stomach in deaths such as these has no hemorrhages characteristic of delirium tremens,[13] nor are such large fatty livers common with delirium tremens, nor is cirrhosis of the liver, as Fahr [4] has also emphasized.

Fahr, in discussing the cause of death from alcohol, mentions the possibility of alterations in the vagus and sympathetic nerves and ganglions within the heart, but his comments do not especially concern the type of disease we are dealing with in which the ratio of liver weight to that of the body is so large, nor does he present evidence of such changes in nerves or ganglions. That alcohol is concerned with changes in the peripheral and central nervous system is generally accepted in connection with both alcoholic neuritis and the Korsakoff syndrome. In another place,[14] one of us (E. R. L.) has an account of gross alterations of the brain with delirium tremens, changes not encountered in the bodies of persons whose deaths are accompanied by the circumstances under discussion.

In these the most conspicuous features are the huge size of the liver and the difficulty in finding liver cells microscopically which from their number and size seem to posses any evidence of glycogen storage consistent with life. This marked fatty infiltration has played a part so important in the classroom work of teaching pathology and has been the subject of so much illustration and description ever since instruction in such details of disease has been practiced, that the alteration may be regarded as familiar to all physicians.

It will be recalled that large globules of fat replace the cytoplasm of the liver cells, and that the nucleus and remaining cytoplasm form a thin crescent ("signet ring") about a part of the periphery of the fat. It is obvious that in such cells there is no considerable store of glycogen. Such livers as these are so loaded with fat that thin slices float in water. A cirrhosis may be present, but is usually not marked. The little present may not be noted grossly, the irregularities otherwise denoting it being smoothed out by the accumulation of fat.

---

13. Hirsch, E. F.: The Gastric Mucosa in Delirium Tremens, Arch. Int. Med. **63**:354, 1914.

14. Sceleth, C. E., and Beifeld, A. F.: Cerebral Edema (Wet Brain) in Chronic Alcoholism, Am. J. Med. Sc. **149**:886, 1915.

It seems to us that any attempt to explain unexpected deaths such as these must include absence of an adequate store of glycogen to meet the requirements of the body for glucose. In only one of these ten patients was chemical examination of the blood made, but in that instance, the sugar, 67 mg. per one hundred cubic millimeters, was significantly low.

Sheep becoming carnivorous when kept in abattoirs and developing an aversion for herbivorous foods, waste and die with fatty livers twice their normal size,[15] and Williams [16] has reported the death of a diabetic patient who had received no insulin, the death, "due to inanition," being accompanied by hypoglycemia and convulsions.

When death is contributed to by hypoglycemia following the use of insulin, convulsions have also been observed; they were not noted, except as mentioned, in the illnesses of the ten patients with these large livers.

It is well known that during heavy drinking of alcoholic beverages, food consumption is frequently reduced to a minimum, and that vomiting may also lessen the value of that taken. The alcohol drunk is oxidized, and the question naturally arises: Is the oxygen available from respiration inadequate to burn both the alcohol and the fat brought to the liver, or is the lessened destruction of fat due wholly or in part to a lowered supply of carbohydrates necessary for the metabolism of the fats?

Such questions are beyond the scope of this article, obviously matters for experimentation. Removal of the liver from animals causes their death, and certainly its replacement by fat to the end that little normal liver tissue remains places such persons in jeopardy, and apparently may either alone cause death or constitute the main contributory factor.

SUMMARY

The weight of the liver, when diseased, as well as the weight of other organs, has special significance when considered with regard to the weight of the body. With an extensive replacement of the liver by fat in persons who drink heavily of alcoholic beverages, death may be entirely unexpected and abrupt and with few symptoms of illness.

In postmortem examinations of such persons, little else than a large fatty liver may be found to explain death.

December 14, 1925.

15. Pages, H.: Histoire d'un monton nügnard; enseignement qu'on tirer, Compt. rend. Soc. de biol. **4**:654-655, 1902.

16. Cited by Woodyatt, R. T.: The Clinical Use of Insulin, J. Metab. Res. **2**:800. 1922.

THE RESULT OF MECHANICAL OBSTRUCTION OF THE HEPATIC VEINS

J. P. SIMONDS
AND
W. W. BRANDES

A method of mechanically constricting the hepatic veins in the dog by means of a rubber tube was described.

Such mechanical constriction caused a sudden fall in arterial blood pressure and a simultaneous rise in pressure in the portal vein. Complete occlusion of the hepatic vein reduced the systemic blood pressure by from 37.5 to 42 per cent; maintaining the occlusion for five minutes or more did not cause a continuous lowering of pressure. On release of the constriction, the arterial pressure rose abruptly to a level 10 to 20 mm. of mercury above the original normal level, and then quickly fell to normal.

Complete occlusion of the hepatic veins during peptone shock caused only a slight further lowering of arterial blood pressure. The injection of peptone while the hepatic veins were occluded resulted in a rather marked further fall in blood pressure due to the dilation of the peripheral vessels by the peptone.

Injection of a foreign serum into a sensitized animal while the hepatic veins were occluded did not result in anaphylactic shock; but, on release of the constriction, the pressure rose quickly to normal and then fell precipitately from anaphylactic shock. When the foreign protein was injected while the hepatic veins were completely occluded, after an interval of one-half to one minute the constriction released for half a minute, and again brought about, the resulting fall in blood pressure was greater than that caused by the occlusion of the hepatic veins alone.

Constriction of the hepatic veins caused a marked increase in the outflow of lymph from the thoracic duct.

December 14, 1925.

A SIMPLIFIED AND QUANTITATIVE ABDERHALDEN REACTION

F. L. PICKOF

The cumbersome and unreliable method of separating the protein split products by dialyzing shells is eliminated. Instead, sterile test tubes are used. Serum and the substrata prepared from placenta, testicle, or carcinoma tissues are placed in test tubes and incubated for twenty-four hours at 37 C. To each tube is added 10 volumes of 97 per cent alcohol. All proteins down to the proteoses are precipitated, while the protein-split products, such as the peptones, polypeptids and amino-acids, as well as the secondary proteoses, remain in solution. The precipitate is coagulated by boiling for one minute, and the fluid filtered. The absolutely clear filtrate from each tube is then tested with ninhydrin. The intensity of the reaction in the tube which contained the placenta substrate is determined by comparing it colorimetrically

with the fluid from the tube with the carcinoma substratum as a standard. In pregnancy the reaction with the placenta substrate is from three to five times as strong as with carcinoma substrate.

December 14, 1925.

DIABETES INSIPIDUS ASSOCIATED WITH SYPHILIS OF THE HYPOPHYSIS

E. B. FINK

This is a report of diabetes insipidus in a man, of twenty years' duration, beginning about five years after a primary syphilitic lesion with symptoms of syphilitic meningitis. At first the polydipsia was extreme and the polyuria enormous. Both improved temporarily under antisyphilitic treatment and were partially controlled by hypodermic injections of pituitrin. Signs of hypophysis dystrophy developed, consisting of loss of body hair, moderate adiposity and atrophy of the genitals. During the few months before death the diabetes insipidus had apparently disappeared.

At necropsy, the changes of interest concerned the hypophysis. It was extremely small, a disk 11 mm. transversely, 7 mm. vertically, and 0.5 mm. thick, including the thickened capsule, which was not to be differentiated from the thickened dura with which it merged. There was no distinct hypophysis, and its location was determined solely by the entrance of the infundibulum into the thickened fibrous tissue. Microscopically, the infundibulum, posterior lobe and pars intermedia were replaced by dense avascular scar tissue. No remains of the anterior lobe were found except in the middle of the mass, where there was glandular tissue about 2 mm. in diameter.

The base of the brain was divided into four blocks, embedded in paraffin and cut in series. The ganglion cells scattered through the hypothalamus and in the tuber cinereum were normal. Nowhere was there round cell infiltration.

In our conception of the pathogenesis of diabetes insipidus, cases in which the lesion is confined to the posterior lobe and infundibulum of the hypophysis cannot be ignored. The hypophysis and midbrain are anatomically united, and in all probability this is true of their function. A lesion in any part of this unit may result in diabetes insipidus, although not invariably. It is just as inconsistent with the facts to state that the hypophysis bears no relation to diabetes insipidus as it is to deny that lesions of the tuber cinereum produce it.

January 11, 1926.

EXPERIMENTAL AMYLOIDOSIS IN MICE*

EFFECT OF DIFFERENT FORMS OF DIET

R. H. JAFFÉ

In a preceding paper[1] the attempt has been made to explain the amyloid degeneration that occurs in white mice after from forty to sixty

* From the Department of Pathology, College of Medicine, University of Illinois, and the Uihlein Memorial Laboratory of Grant Hospital, Chicago.

1. Jaffé: Amyloidosis Produced by Injections of Proteins, Arch. Path. **1**:25 (Jan.) 1926.

injections of foreign proteins on the base of an acquired hypersensibility against the injected substances. The following facts warrant this explanation: The onset and the development of the degenerative changes depend mainly on the number of injections. The amount of the single injection is not essential, nor is it the kind of protein that is being used. In recent experiments typical amyloidosis has been produced by means of crystallized egg albumin. In the sensitized organism the reinjected protein causes an abnormal cleavage of body tissue. Cleavage of body tissue for a long time has been known to be the principal cause of amyloidosis. Observations made by Letterer and published since the first paper went to press, support this explanation. Letterer [2] described amyloidosis in mice following the implantation into the peritoneal cavity of sterile pieces of spleen, liver, kidney and heart obtained from mice. He concludes that the resorption of substances liberated from the implanted tissue that becomes necrotic leads to destruction of body proteins. The toxic effect of sterile autolysis in vivo has also been shown by Mason and Davidson.[3]

Objections to the possibility of producing amyloidosis by injecting nutrose have recently been made. While Strasser [4] and Smetana [5] fully confirmed Kuczynski's [6] observations on amyloid, Ushino,[7] a pupil of Aschoff, was less successful. He emphasizes bacterial contamination. This, however, could be excluded in our experiments, since cultures made from the muscles into which the injections had been made remained sterile. Ushino discusses also the possibility that the injections into the muscles may cause necrosis and that the resorption of this necrotic tissue may lead to amyloidosis. This question could easily be tested. Six mice received daily injections with 0.5 cc. of sterile saline solution. They were killed after the seventieth injection; none showed amyloid. From these experiments another conclusion can be drawn, namely, that the insignificant amount of killed bacteria or of bacteria products probably present in the salt solution used to dissolve the proteins can be neglected. A spontaneous amyloidosis in apparently normal mice, as mentioned by Wells,[8] was not observed. One control developed a spontaneous epithelioma of the ear, and two others had abscesses in the abdominal wall. They were the only controls that showed amyloid.

---

2. Letterer: Verhandl. d. deutsch. path. Gesellsch. **20**:301, 1925.
3. Mason and Davidson: J. Lab. & Clin. Med. **10**:622 and 997, 1925.
4. Strasser: Ztschr. f. d. ges. exper. Med. **36**:381, 1923.
5. Smetana: Bull. Johns Hopkins Hosp. **37**:383, 1925.
6. Kuczynski: Klin. Wchnschr. **2**:722 and 2193, 1923.
7. Ushino: Verhandl. d. deutsch. path. Gesellsch. **20**:304, 1925.
8. Wells: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 472.

A survey of the literature on experimental amyloidosis reveals that no attempt so far has been made to prevent it. Doederlein, Klinge and Wacker[9] recorded that painting white mice with coal tar frequently causes amyloidosis. If, however, the mice were fed cholesterol and fat, they usually remained free from amyloid (Klinge and Wacker). On the other hand, a diet rich in proteins is said to cause amyloidosis (Kuczynsky, Smetana). Smetana used Swiss cheese and Kuczynsky cheese and egg albumin, but they did not investigate whether other forms of protein diet may have a similar effect.

A study of the question whether lipoids may influence the formation of amyloid is suggested through the observations of Jobling and Petersen[10] and of Pfeiffer.[11] These investigators found a certain protective action of lipoids in intoxications associated with an abnormal cleavage of body proteins.

The mice subjected to the protein injections were fed fat diets of different composition. Injections of lipoids were not used, because the total number of injections would have been too great. After having learned of Klinge's and Wacker's findings, cholesterol was added to the fat mixtures. A group of mice was kept on a diet rich in proteins while the control mice were fed the standard diet consisting of white bread, oats and skimmed milk diluted with equal amounts of tap water.

METHODS

The fat diet consisted of 12 Gm. wheat flour, 60 Gm. skimmed milk diluted with equal parts of tap water, 6 Gm. lard, 3 Gm. fresh butter, and 0.5 Gm. cholesterol. The cholesterol was ground up with the lard and butter. The whole mixture formed a paste which the mice ate eagerly. Each mouse received daily 3 or 4 Gm. of the paste containing about 20 mg. of cholesterol. Every sixth day plain diet was given. Fresh tap water was supplied ad libitum. The mice of the protein group received dried beef heart powder. The powder was moistened with tap water, and a dough was made with the aid of a little yeast. The daily ration was 2 or 3 Gm. and tap water. This diet was also taken very well, and the trays on the next morning were always empty. Once a week stock diet was given.

The mice were kept in separate cages. After having become accustomed to the new diet, they received daily injections with 0.5 cc. of a 3 per cent nutrose solution. Four mice of each group did not receive injections and served as controls.

It was found that the formation of extensive general amyloidosis could be hastened by preparing the nutrose solution in a different way than that described in the first paper. The nutrose was dissolved in saline solution at 50 C. and

9. Doederlein, in Klinge and Wacker: Krankheitsforschung **1**:257, 1925.
10. Jobling and Petersen: Ztschr. f. Immunitätsf. **24**:219 and 292, 1916.
11. Pfeiffer: Krankheitsforschung **1**:407, 1925.

immersed in boiling water for fifteen minutes. Using this solution, general amyloidosis was constant after fifty injections.

A series of mice first received the nutrose injections, and they were put on fat diet after the seventeenth, twenty-ninth, thirtieth and thirty-second injection, the injections being continued.

The first animals were killed after the fifty-fifth injection. At this time amyloidosis in 100 per cent of the controls on plain diet was found. The mice were anesthetized with ether, and the heart was exposed by an incision through the sternum. Blood was drawn with the aid of a tuberculin syringe and allowed to run into a graduated centrifuge tube containing 30 mg. of lithium oxalate. Blood sufficient for the determination of the nonprotein nitrogen (Folin and Wu's method) and of the cholesterol (Bloor's second method) was usually secured; 0.5 cc. of blood was used for the nitrogen determination and 0.6 cc. for the cholesterol. After precipitating the proteins, and after extracting the lipins for two hours at 50 C., the tubes were centrifuged at high speed, and the perfectly clear and colorless supernatant fluid was used.

The time between death and the last injection was twenty-four hours; that between death and the last feeding twelve hours. In a special group referred to below, the time between feeding and death was two, three and four hours.

CHOLESTEROL FAT DIET

Cholesterol Metabolism of the Normal Mouse.—Feeding the omnivorous mouse cholesterol (dissolved in a sufficient amount of fat in order to secure optimal resorption in the intestine) does not produce the hypercholesterinemia that is typical of the herbivores, especially the rabbit (table 1). There is only a slight transient rise of the blood cholesterol following the meals. After the animals became accustomed to this diet, no increase of the cholesterol of the blood at any time was noted. According to the current view, it is the quick elimination of the cholesterol through the liver that prevents its accumulation in the blood of the omnivores. This quick elimination also accounts for the fact that the reticulo-endothelial cells of the mouse do not store the cholesterol.

The mice on cholesterol fat diet show a marked increase of the subcutaneous fat tissue and compact layers of fat tissue about the kidneys and the sex organs.

Of the internal organs, the liver takes part in the storage of the fat (fig. 1). The liver of the mouse normally plays an important rôle in the fat metabolism, and the liver cells during digestion always contain fat droplets (Wolff [12]). The fat content is much greater and persists much longer when cholesterol fat diets are given. The fat takes a different form, namely, the droplets are much larger and more or less completely fill the cells. When tested between crossed Nicols many double refracting crystals are found. The epithelial cells of the

12. Wolff: Virchows Arch. f. path. Anat. **252**:297, 1924.

bile ducts remain free from fat; so do the Kupffer cells, which reveal signs of proliferation such as many mitotic figures and formation of intracapillary nodules.

The histologic examination of the small intestine at the height of digestion shows the well-known pictures of fat resorption through and between the epithelial cells. The stroma of the villi is filled with single and double refracting lipoid droplets of different size and shape. Much optically active fat is found in the central lymph space. The finest fat granules are observed in the blood capillaries underneath the epithelium, which are greatly distended during digestion. The droplets stand out distinctly between and about the red blood corpuscles. Great care was taken to avoid an artificial squeezing of fat into the capillaries. The pieces before sectioning were rinsed with saline solution and were cut in the direction from the muscularis toward the internal surface.

TABLE 1.—*Results of Chemical Examination of Blood*

Group	Cholesterol		Nonprotein Nitrogen	
	Average	Range	Average	Range
Normal controls	135	120–151	27	20– 35
Fat controls	134	112–151	28	22– 32
Fat nutrose	137	131–144	37	32– 42
Beef heart controls	136	120–146	60	39– 77
Beef heart nutrose	125	110–158	83	46–184
Nutrose controls	123	116–130	54	39– 77

The fat granules were present only in the subepithelial capillaries. They seemed to disappear toward the center of the villi, and no fat was found in the central vein nor in the veins of the submucosa. It appears that the fat, after having entered the blood stream, changes into an invisible form.

The possibility of fat absorption through channels other than the lymphatics has been suggested also by the chemical studies of Bloor,[13] D'Errico,[14] Eckstein,[15] Hamburger,[16] Hall,[17] Joannovicz and Pick[18] and Munk and Friedländer.[19]

No changes in other organs resulted from the peculiar diet. In the beginning of the fat diet, lipoid granules in the epithelial cells of the tubuli contorti were found. They disappeared later. No increase of

13. Bloor: J. Biol. Chem. **23**:317, 1915.
14. D'Errico: Arch. di fisiol. **4**:513, 1907.
15. Eckstein: J. Biol. Chem. **62**:737, 1925.
16. Hamburger, in Eckstein (footnote 15).
17. Hall: Ztschr. f. Biol. **62**:1923.
18. Joannovicz and Pick: Verhandl. d. deutsch. path. Gesellsch., 1910.
19. Munk and Friedländer, in Eckstein (footnote 15).

fat in the cortex of the suprarenals could be found. Schmidt [20] mentioned that double refracting fat usually appears in the cortex of the suprarenals of cholesterol fed mice. But the cortex of the suprarenals of the mouse normally contains varying amounts of microscopically visible cholesterol compounds, and this often to the same extent as after feeding cholesterol. The same is to be said about the sweat glands. The size of the component cells and the amount of anisotropic fat globules in the cells are not greater after cholesterol diet than they are before. The fatty layer covering the epidermis is of the same thickness in both controls and cholesterol mice. In the lungs, a larger amount of fat-carrying cells was sometimes found in the alveolar septums. The fat was not double refracting.

Cholesterol Fat Diet and Nutrose Injections.—The diet rich in cholesterol and fat increases the resistance of the mouse against the harmful effect of long continued intramuscular injections of foreign proteins. While the mice on plain diet develop extensive amyloidosis after from forty to fifty injections, the animals fed the cholesterol paste after seventy injections are still free (tables 2 and 3). The protecting action of the lipins is but a relative one, for even the cholesterol mice show amyloid degeneration after more than seventy-five injections. The changes, however, are less extensive than they are in the controls. None of the mice of the cholesterol group died spontaneously, whereas 30 per cent of the controls died between the thirtieth and sixtieth injection.

Feeding cholesterol and fat when started after the animals have been sensitized does not protect (table 2).

The influence of the cholesterol fat diet on the changes stipulated by the nutrose injections is also evident from the behavior of the nonprotein nitrogen of the blood (table 1).

The nonprotein nitrogen after from thirty to forty injections of nutrose into mice on plain diet is found to be constantly higher than normal. Sometimes the increase is only slight; sometimes it is more than three times normal. This increase appears later when fat diet is given. For example, the nonprotein nitrogen of a mouse that was kept on plain diet and showed advanced amyloidosis after fifty-three injections was 76 mg. per hundred cubic centimeters of blood. A cholesterol mouse with seventy injections and still free from amyloid gave 32 mg., and another mouse with eighty-five injections and mild general amyloidosis 42 mg.

The injections of nutrose at first do not affect the storage of fat in the physiologic fat deposits and the accumulation of lipins in the

20. Schmidt: Virchows Arch. f. path. Anat. **253**:432, 1924.

liver. Thus, the liver cells after from fifty to sixty-five injections still are filled with droplets of neutral fat and double refracting spherocrystals (fig. 2).

Antedating the amyloid degeneration for a short time, the fat starts to disappear from the physiologic deposits and from the liver cells. The difference between the microscopic fat content of the liver after the fifty-sixth and the eighty-fifth injection is striking. After fifty-six injections, the liver cells contain just as much fat as they do in the cholesterol fed controls. After eighty-five injections, most of the fat is gone (fig. 3). Although some fat still is present, it is of a different

TABLE 2.—*Fat Diet*

Days on Diet	Number of Injections	Amyloid in				
		Spleen	Liver	Kidney	Suprarenal	Intestine
63	55	0	0	0	0	0
71	60	0	0	0	0	0
78	65	0	0	0	0	0
82	68	0	0	0	0	0
85	70	0	0	0	0	0
96	78	Trace	0	0	0	0
102	85	++	+	Trace	+	Trace
20	52	+++	++	+	++	+
26	55	++	++	+	+	+
30	60	+++	++	+	+	+
48	65	+++	++	++	+	+

TABLE 3.—*Plain Diet*

Number of Injections	Amyloid in				
	Spleen	Liver	Kidney	Suprarenal	Intestine
30	+++	+++	++	++	+
37	+++	+++	++	+	+
53	+++	++	+++	++	+
66	+++	++	+	+	+

character and morphology. The droplets are small. They give no or little double refraction (fig. 4). The fatty changes are associated with signs of cellular disintegration such as vacuolization or hyalinization of the cytoplasma and swelling and pyknosis of the nuclei. No changes of the nuclei of the liver cells apart from the mechanical deformation are observed as long as the cells are filled with stored fat.[21]

The accumulation of fat in the liver cells is also greatly impaired when the cholesterol fat feeding is started after the twentieth injection. At no time, even not as early as after thirty-five injections, do the liver cells contain larger amounts of lipoids.

21. The cholesterol content of the suprarenal cortex is not influenced by the nutrose injections. Even when amyloid is found in the zona reticularis, the cells of the fasciculata are filled with single and double refracting fat droplets.

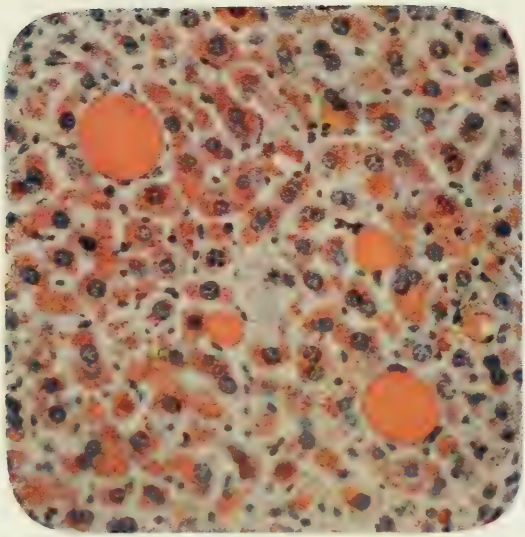


Fig. 1.—Liver of a mouse which was kept on cholesterol fat diet for ninety-nine days; liver cells are crowded with fat droplets. Note single very large fat drops; no fat in Kupffer cells. Ten per cent liquor formaldehydi, sudan III, hematoxylin.

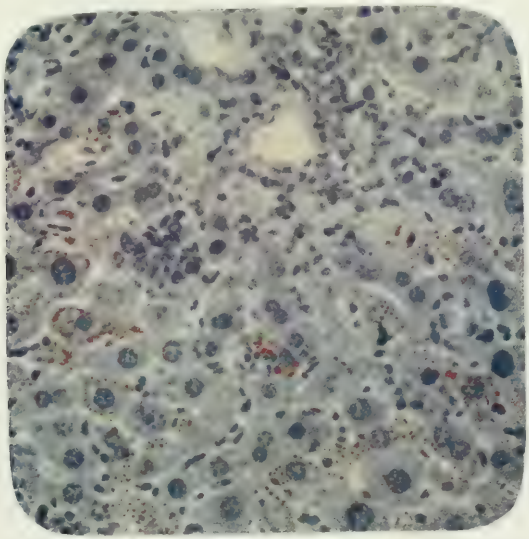


Fig. 3.—Liver of mouse kept on cholesterol fat diet for one hundred and two days and receiving eighty-five injections of nutrose. Liver cells contain very little fat; many are free from it. Pyknosis of nuclei in some cells. Small lipoid granules in the Kupffer cells. Beginning pericapillary amyloidosis. Ten per cent liquor formaldehydi, sudan III, hematoxylin.

One may suggest that the sick mouse does not take sufficient food in order to secure a visible fat storage in the liver. But the mice with beginning amyloidosis eat the fat paste just as well as do the normal mice, and when killed during digestion the villi of their small intestine are crowded with fat droplets.

The marked decrease of the cholesterol stored in the liver cells of the mice fed this lipin that occurs after very long-continued nutrose injections is not associated with a persistent rise of the cholesterol in

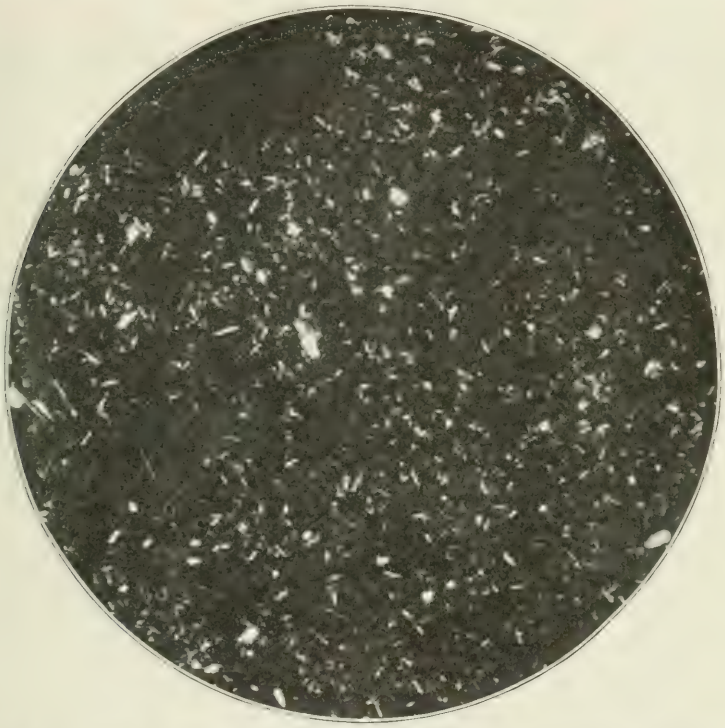


Fig. 2.—Liver of mouse kept on cholesterol fat diet for seventy-one days that had received sixty nutrose injections. Many double refracting crystals of cholesterol esters in the liver cells. Ten per cent liquor formaldehydi; unstained frozen section.

the blood. Only when the mice are killed from three to four hours after the feeding is there a distinct rise of the blood cholesterol. It then amounts to 180 mg. and more; but from ten to twelve hours later it is again normal. The elimination of the cholesterol is apparently delayed but not completely impaired.

The Fat Content of Amyloid.—The amyloid produced experimentally in animals as well as that of human beings contains varying amounts of

fat microscopically demonstrable with the aid of fat stains, such as sudan III and Nile-blue sulphate. The fat either appears as small droplets or as finest dustlike granules. Sometimes the amyloid is found free from fat. In the liver, much fat is found in the amyloid about the portal capillaries, while it is scanty in or absent from the amyloid in the wall of the larger vessels. Kuczynski, in accordance with his conception of the origin of the amyloid, assumes the fat to be precipitated out of the tissue fluids by the coagulating amyloid. This explana-

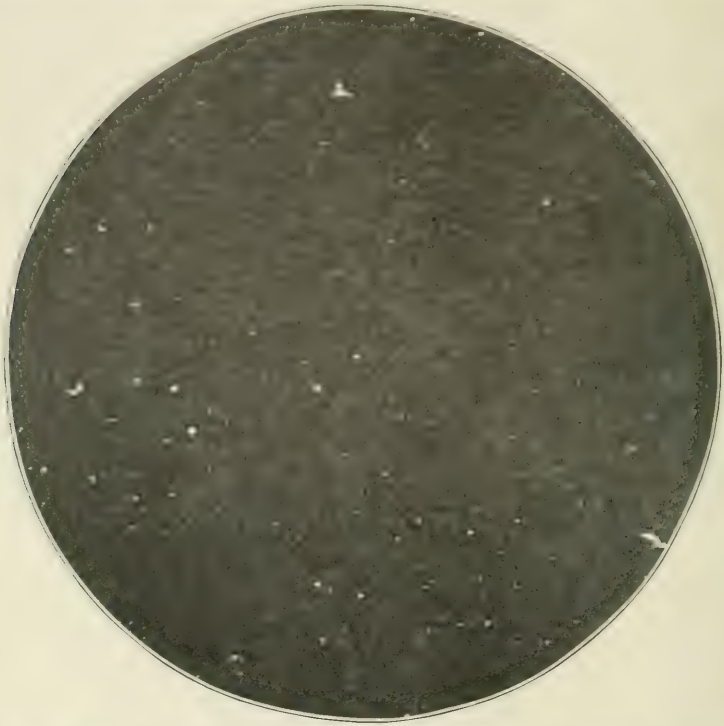


Fig. 4.—Same as figure 3. Very few and small double refracting crystals as compared to figure 2. Ten per cent liquor formaldehydi; unstained frozen section.

tion does not take into consideration the fact that in the same microscopic field the amyloid in some places may be full of fat droplets, while in others it may be free from fat. This holds true for both human and animal amyloid.

Comparing the different stages of amyloid degeneration, it can be learned that it is the amount of fat in the cells embedded with the amyloid that determines the fat content of the latter. The cells walled off from the surrounding tissue by the amyloid became atrophic. They shrink

and disappear. When they contain fat it remains visible and can often be seen arranged about the remnants of a pyknotic nucleus. The endothelial cells of the liver with amyloid degeneration usually are filled with lipoid droplets. Therefore the pericapillary amyloid shows much fat. The amyloid in the wall of the larger vessels contains little or no fat, because it has no direct relation to the fat-carrying cells.

The cholesterol fat diet does not increase the lipoid content of the amyloid.

MEAT DIET

The effect of high protein diets has repeatedly been studied, especially from the standpoint of producing renal vascular lesions (Newburgh, Newburgh and Clarkson,[22] Newburgh and Marsh,[23] Polvogt, McCollum and Simmonds,[24] Miller[25]). Most of the experiments were made on rabbits and rats. Rats seem not to be affected by protein feeding (Miller). Mice also stand the high protein diet very well. They gain in weight and do not seem to be sick at any time, although the nonprotein nitrogen content of their blood is distinctly higher than normal (table 1). The examination of the internal organs shows an enlargement of the spleen, liver and kidneys. No histologic changes are found in the kidneys nor in any other organ. With regard to Kuczynski's and Smetana's experiments with cheese feeding, it was of special interest that none of the control mice on beef heart powder diet developed amyloidosis, although this diet was given for more than 100 days.

Meat Diet and Nutrose Injections.—From Kuczynski's observations, it was to be expected that the meat diet would intensify or hasten the amyloid degeneration. But the meat diet did not only not favor the amyloidosis, it even protected the mice against it, and this to the same extent as did the cholesterol fat diet. Thus, one of the mice fed on meat showed no amyloid degeneration after as many injections as eighty-seven (table 3).

The chemical examination of the blood of the mice fed the high protein diet and receiving injections of nutrose, reveals that there is no constant parallelism between the increase of the nonprotein nitrogen

22. Newburgh and Clarkson: Production of Arteriosclerosis by Diets Rich in Animal Proteins, J. A. M. A. **79**:1106 (Sept. 30) 1922; Arch. Int. Med. **24**:351, 1919.

23. Newburgh, Marsh, Clarkson and Curtis: Dietetic Factor in Etiology of Chronic Nephritis, J. A. M. A. **85**:1703 (Nov. 28) 1925. Newburgh and Marsh: Renal Injuries by Amino-Acids, Arch. Int. Med. **36**:682 (Nov.) 1925.

24. Polvogt, McCollum and Simmonds: Bull. Johns Hopkins Hosp. **34**:168, 1923.

25. Miller: J. Exper. Med. **42**:877, 1925.

in the blood and the appearance of amyloid in the organs. Thus, the nonprotein nitrogen of a mouse still free from amyloid after eighty-seven injections was 76.9 mg., while it was 60 mg. in a mouse with beginning amyloidosis after sixty injections. The most marked increase of 184 mg. per hundred cubic centimeters of blood was found in a mouse with general amyloidosis after eighty injections.

COMMENT

The experiments reported prove the possibility of protecting mice for a considerable length of time against the harmful effect of repeated injections of foreign proteins which otherwise lead to amyloidosis in from five to eight weeks.

The mice are rendered more resistant by feeding large amounts of cholesterol and fat. They are protected as long as they are able to

TABLE 4.—*Protein Diet*

Days on Diet	Number of Injections	Amyloid in				
		Spleen	Liver	Kidney	Suprarenel	Intestine
52	50	0	0	0	0	0
70	57	0	0	0	0	0
83	74	+	0	0	0	0
98	80	+++	++	+	+	+
106	87	0	0	0	0	0

store the fat. The injections, however, finally cause the mice to lose this ability. The fat diet is then no longer effective, and amyloid appears in the different organs. It takes about twice as many injections to produce amyloid in a cholesterol fed mouse as it takes for mice on plain diet.

The most striking and the most significant changes are found in the liver whose cells take normally a part in the storage of cholesterol and neutral fat when large quantities of these substances are given with the food. After about the seventieth injection, the stored lipins gradually disappear from the liver cells. When amyloidosis starts later, there remains but little cholesterol and fat in the liver cells, or the cells are free from double refracting material. The fat which still can be found does not exceed the amount observed in the mice on plain diet with beginning amyloidosis.

Since the storage of excessive cholesterol and fat of the food is a normal function of the liver of the mouse, the disappearance from the liver cells of these substances preceding the onset of the amyloidosis suggests an impairment of the functional activity of this organ, associated

with the metabolic disturbances causing amyloid degeneration. The disturbed liver function also explains the marked hypercholesterinemia of the mice with amyloidosis during digestion.

The cholesterol metabolism in cases of human amyloidosis has not been investigated, as, in general, metabolic studies in amyloid degeneration during life still are lacking. I think that such studies may help more to a solution of this intricate problem than the chemical analysis of the amyloid substance itself and the most careful examination of its morphology.

Some observations in human amyloidosis can best be explained on the basis of a disturbed cholesterol metabolism. The liver does not yield peculiar microscopic findings. When amyloid is formed in the liver, it often is associated with isotropic fatty changes. Large amounts of cholesterol, however, are found in the kidneys showing advanced amyloid degeneration (Danish,[26] Fahr,[27] Munk[28]). The anisotropic fatty infiltration of the amyloid kidney is excelled only by the lipoid nephrosis (Fahr). Munk even emphasizes the close relationship between lipoid nephrosis and amyloid degeneration. Windaus made his fundamental chemical analysis of cholesterol esters on amyloid kidneys.

What may bring about the accumulation of cholesterol compounds in amyloid degenerated kidneys has not yet been determined (Danish). Our observations offer the explanation that it is a disturbed liver function that causes an alteration of the cholesterol metabolism with an accumulation of the cholesterol in the blood (Danish). That the cholesterol is deposited in the kidney may partly be due to local circulatory disturbances resulting from the amyloid degeneration of the blood vessels. Circulatory disturbances favor the local precipitation of cholesterol (Lubarsch). Furthermore, an excretion of the cholesterol through the kidneys can be assumed on the basis of the studies of Gardner and Gainsborough.[29] Also in the mice with advanced renal amyloidosis, double refracting lipins were found in the epithelial cells of the convoluted tubuli.

No satisfactory explanation for the protection of the mice by feeding cholesterol can yet be given. The addition of cholesterol to the food is important, because the plain fat diet hardly increases the resistance of the mouse. Whether it is the storage of the cholesterol compounds in the liver that is essential, I do not know; but the drop of the body

26. Danish: Verhandl. d. deutsch. path. Gesellsch. **20**:307, 1925.
27. Fahr: Handbuch der path. Anat. u. Histol. **6,** G. Springer.
28. Munk: Pathologie und Klinik der Nephrosen, Urban and Schwarzenberg.
29. Gardner and Gainsborough: Biochem. J. **19**:667, 1925.

weight and the increase of the nonprotein nitrogen of the blood is delayed as long as the liver cells are filled with the lipins.

Feeding beef heart powder gives results similar to the cholesterol diet. According to Newburgh, beef heart powder contains about 81 per cent of protein. Cannon,[30] discussing the facts affecting the protein equilibrium, recently made the statement that "there has developed a considerable body of evidence that with abundant protein feeding the hepatic cells can store protein just as they can store glycogen" (and fat—author's remark). The stored protein apparently displays a protecting action, as do the cholesterol compounds. Or are the lipins of the beef heart muscle the important part? The total ether extract, lipins of all kinds, of the heart is between 2.86 and 3.73 per cent. Most of the lipin is phospho-lipin (Mathews[31]). Cholesterol is about 0.2 per cent of the dried muscle substance, and phosphatids are 8 per cent of the dried heart (Rubner[32]). These quantities are too small to be of any significance.

The question will arise as to what may be the cause of the differences between the results of the experiments with beef heart and those with cheese. Feeding cheese, as reported by Kuczynski and Smetana, produces amyloid; beef heart powder may prevent it.

The meat powder apparently is a more suitable form of food rich in protein than is cheese. When Swiss cheese and bread are given, the mice often refuse the cheese after several days and rather starve than take it (Heiberg[33]). They frequently suffer from intestinal disturbances and have more or less liquid stools. The intestinal mucosa is found to be edematous, with swollen and desquamated epithelium. It seems to me that the chronic enteritis resulting from the cheese diet, and not the flooding of the body with the split products of an abnormal protein metabolism, causes the amyloid degeneration. The mice that receive the beef heart do not show signs of intestinal irritation. They remain, therefore, free from amyloid.

CONCLUSIONS

Feeding (*a*) cholesterol and fat, or (*b*) dried beef heart powder increases the resistance of mice against the toxic action of long continued injections of foreign proteins. Thus, the formation of amyloid can be delayed for a considerable length of time.

---

30. Cannon: Am. J. M. Sc. **171**:1, 1926.

31. Mathews: Physiological Chemistry, ed. 3, New York, William Wood & Company.

32. Rubner: Klin. Wchnschr. **4**:1849, 1925.

33. Heiberg: Centralbl. f. allgem. Pathol. u. path. Anat. **36**:433, 1925.

The fat diet, however, is effective only when started together with the injections. If there is an interval between them, the beginning of the injections preceding the diet for more than two weeks, no protection of the mice can be noted.

The experiments with cholesterol reveal an alteration of the cellular activity of the liver immediately preceding the onset of the amyloid changes. The ability of the liver cells to store the cholesterol as double refracting spherocrystals is greatly reduced.

The difference between the effect of feeding cheese and beef heart powder is explained on the basis that cheese causes a chronic irritation of the intestine and thus may lead to amyloidosis, while the beef heart is a more suitable form of protein diet, does not affect the intestinal mucosa, and may even prevent amyloid degeneration.

January 11, 1926.

AN EXPERIMENTAL METHOD FOR THE STUDY OF THE BACTERIAL FLORA AND THE HYDROGEN-ION CONCENTRATION OF THE GASTRO-INTESTINAL TRACT

LLOYD ARNOLD

A method was devised for fixing certain segments of the intestinal tract to the anterior abdominal wall in such a way that the content of a particular segment could be aspirated for chemical and bacteriologic study. The duodenum was found to contain relatively few bacteria; the H-ion concentration varied from p_H 5.2 to 6.2. The upper part of the jejunum contained the same bacterial flora; the H-ion concentration was a little more alkaline—p_H 5.5 to 6.6. The lower jejunum was found to contain a richer bacterial flora, the gram-negative bacilli were usually encountered in this region, and the H-ion concentration approached neutrality. The ileum had a mixed bacterial flora, similar to that found in the feces; the H-ion concentration was neutral or slightly alkaline.

When alkaline, buffered salt solution (p_H 8-9) is injected into the duodenum, the bacterial flora changes to the type usually found in the ileum. Acid buffered solutions do not change the bacterial flora. When the gastric acidity was depressed by the elevation of the temperature, the duodenal bacterial flora was found to be fecal in type.

A peripheral leukocytosis was associated with an alkalinization of the duodenum. The maintenance of the normal H-ion concentration and the normal bacterial flora of the content of the duodenum and upper jejunum are dependent to a great extent on the normal gastric secretion.

January 11, 1926.

THE COMPARATIVE PATHOLOGY OF THYROID TUMORS

MAUD SLYE
HARRIET F. HOLMES
AND
H. GIDEON WELLS

A study of the literature on the occurrence of tumors of the thyroid in animals discloses that while malignant thyroid neoplasms are not uncommon in man, they seem to be extremely rare in all other animals except the dog family. In dogs the thyroid seems to be one of the commonest sites of cancer, and, furthermore, nearly all of the scanty number of cases of thyroid malignancy observed in wild animals have been observed in canines, chiefly wolves. A few cases have been observed in horses, but practically none in any of the domestic food animals. Only two cases have been reported in birds. A few cases have been reported in rats. A striking feature of thyroid cancer is that many of the growths show histologic characteristics suggesting in part carcinoma and in part sarcoma, and this is equally true for the cancers observed in the lower animals as well as in man. Hitherto no case of thyroid tumor seems to have been reported in mice. In about 51,700 necropsies in the Slye stock of mice there have been but seventeen animals in which noticeable enlargement of the thyroid was observed. Five of these had simple goiters. Twelve had malignant tumors, of which two seemed to be sarcomas and six carcinomas, and four exhibited mixed characteristics of sarcoma and carcinoma.

February 8, 1926.

FUSOSPIROCHETAL ABSCESS OF THE TONSILS

I. PILOT

In the consideration of tonsillar infections by *B. fusiformis* and Vincent's spirochete, the most common condition is the acute angina. These organisms can be demonstrated readily in large numbers in smears made from the membrane. A considerable number of persons (30 per cent or more) harbor in their tonsils granular, actinomyces-like masses, made up largely of these organisms. The presence of these granules excites little or no cellular reaction. A chronic inflammation may exist if the granules distend the crypts. In the course of routine examination of many hundreds of tonsils, chronic abscesses were often encountered, but in only three instances were the lesions associated with these organisms.

Case 1.—The tonsils were equal in size, 2 cm. long, 1.7 cm. wide and 1.5 cm. thick. Under the capsule of one, a gray bulging occurred which on section proved to be an abscess 8 mm. in diameter, filled with foul smelling pus. Smears revealed numerous fusiform bacilli, spirochetes and cocci. Aerobic cultures contained *Streptococcus viridans* and the anaerobic streptococci together with fusiform bacilli. The opposite tonsil contained a smaller abscess under the capsule, 5 mm. in diameter, filled with odorless pus. Smears revealed strepto-

cocci and no anaerobes. In microscopic sections of the putrid abscess, a chronic inflammatory reaction was present. The cavity was lined by an irregular, thin epithelium and filled with numerous leukocytes, débris and masses of bacteria. The capsule was markedly thickened, and contained small foci filled with leukocytes. In Levaditi preparations the bacilli and spirochetes appeared in the abscess wall.

Case 2.—The tonsils measured 2 cm. long, 1 cm. wide and 1 cm. thick. On section there was a distinct increase in connective tissue and a dilated crypt filled with foul smelling pus. Smears revealed the anaerobes and cocci. The opposite tonsil had some purulent exudate in a crypt with no odor, although stained preparations contained a moderate number of fusiform bacilli and spirochetes.

The reaction in microscopic preparations was of a chronic inflammatory character with a distinct increase in connective tissue. In Levaditi preparations the bacilli and spirochetes formed masses in the exudate of the crypt, and only a few were found in the lining of the cavity.

Case 3.—These were large tonsils, 2.5 cm. long, 1.5 cm. wide and 1.5 cm. thick. On section an abscess cavity filled with a foul exudate was found. Smears revealed a mixture of bacilli, spirochetes and cocci. In the microscopic sections a distinct abscess with marked necrosis of the wall was observed, communicating with a crypt. In Levaditi preparations the necrotic region was filled with many bacilli and spirochetes, but there was no invasion of the contiguous tissue.

A fourth instance was observed in a medical student who complained of recurrent sore throat with foul breath. His tonsils had been removed, but the sore throat persisted. On examination, there appeared considerable lymphoid tissue in the upper portion of the tonsillar fossa, with a foul purulent discharge oozing from the surface. A wire loop introduced into the region led into a small abscess cavity containing foul pus. Smears demonstrated numerous bacilli, spirochetes and cocci.

A chronic form of fusospirochetal infection of the tonsil is described. The exudate is usually foul smelling and contains streptococci in addition to the anaerobes. The lesion is a chronic abscess, and in one instance associated with necrosis of the tissue lining the abscess cavity.

February 8, 1926.

TORSION OF THE LEFT FALLOPIAN TUBE WITH SPONTANEOUS AMPUTATION, AND FIBROMA OF THE RIGHT OVARY

C. W. BARRETT
AND
A. F. LASH

Spontaneous amputation of fallopian tubes, especially normal, is a rare postmortem and operative finding. Twenty-seven cases have been observed postmortem, the first being that of Morgagni, 1748. After operative procedures were undertaken, surgical reports followed, and since the first in 1892 by

Martin, twenty-three have been recorded. The interpretation of the mechanism in the individual cases is interesting.

The incidence of fibroma of the ovary is 1.3 to 2 per cent of ovarian tumors. Shochet found eighty reports in the literature up to 1924. It is of no clinical significance except when pressing on surrounding structures or when it is malignant. This report is made because of the rarity.

E. M., a white woman, aged 40, entered the gynecologic service of Dr. Channing W. Barrett at Cook County Hospital on Oct. 13, 1925. She complained of pain in the lower part of the abdomen and of leukorrhea. The onset and course was as follows: While preparing breakfast on Oct. 10, 1925 (three days before admission), she had suddenly a severe knifelike pain in the left lower part of the abdomen. She went to bed and remained there the entire day. The pain gradually subsided after several hours, and became dull and aching. She vomited three times shortly after the onset of the pain. The next day she was able to get up and about, although the pain continued. Hot water bag relieved the pain a little. There was also painful urination, backache and loss of appetite. The leukorrhea, present for one year, was profuse. Her general systemic condition was good.

Menses began at the age of 12, twenty-eight day type, four day period, the last period being September 26 to 30, 1925. She married at the age of 19, had one full term pregnancy with spontaneous delivery. She married again at the age of 28, after divorcing her husband. A full term pregnancy with spontaneous delivery followed. A third pregnancy terminated at the third month by abortion, which was completed by a curettage. Following this operation she had fever and was confined to bed for two weeks.

By physical examination were found a slight tenderness in the iliac fossae, a relaxed pelvic floor with a cystocele and a rectocele, and a prolapsing uterus with adnexitis. A vaginal hysterectomy, pelvic floor repair and removal of the tumor of the right ovary by laparotomy was done.

The tissue contained the uterus, two fallopian tubes and a right ovarian tumor. The uterus was 6 cm. long, 5 cm. wide and 5.5 cm. thick. The peritoneum was smooth and glistening. The fundus had the normal rounded form and from the left cornu extended the conical stump of the left fallopian tube, which was soft, 1 cm. in length. The uterine wall was 1.6 cm. thick, and the myometrium was firm. The endometrium was normal in appearance and thickness. The cervix at the external os was firm and nodular from the multiple healed lacerations and nabothian cysts. The endocervix was smooth and covered with clear mucus.

The left fallopian tube was a bluish-black, twisted mass. The length of the tube was 12.5 cm., and the diameter varied from 2 mm. at its conical uterine end to 2 cm. at the fimbriated end. The peritoneal surface was smooth and the tube was firm. The uterine end was closed and conical, while the fimbriated end was open. Longitudinal section of the tube revealed a thick, dark red wall, the lumen filled with clotted blood and the longitudinal folds visible after removing some of the blood. The vessels in the part of the mesosalpinx attached to the tube were thrombosed.

The right fallopian tube was 12 cm. long and 1 to 2.5 cm. in diameter. It was firm, thick and bound together by adhesions, but the fimbriated end was open. The endosalpinx was unchanged.

The tumor representing the right ovary was hard, smooth, round, flattened anteroposteriorly 6 cm. in diameter and 4 cm. thick. The surfaces made by cutting were firm, white fibrous tissue.

In microscopic sections of the spontaneously amputated tube there was a recent hemorrhage without inflammation. The muscular fibers of the wall were separated by masses of red blood cells and edema, while the vessels were markedly dilated. In the endosalpinx the infiltration with blood cells was marked.

Microscopic sections of the corpus showed the endometrium to be in the resting stage. Both endometrium and myometrium were hyperemic. There were masses of leukocytes in some of the glands. In one subperitoneal region there was some edematous fibrous tissue with a mass of leukocytes.

The tumor of the ovary contained only spindle-shaped connective tissue cells.

The tissue changes in this patient, then, were a fibroma of the right ovary, healed right perisalpingitis and spontaneous amputation of the normal left fallopian tube, into which there was a recent hemorrhage, resulting from torsion. In this instance, the spontaneous amputation of the tube was certain as there was no history or evidence of operation in these tissues, and the twisted tube was further confirmation. However, to interpret the mechanism which produced the torsion and spontaneous amputation requires further study.

Constipation produced congestion in the pelvis which, according to Payr's hemodynamic theory, may initiate a twisting of an organ with a pedicle. Further, the prolapsing uterus brought the left cornu at a level or below that of the infundibulopelvic ligament, thereby narrowing the width of the broad ligament or pedicle. Thus the twisting of the congested tube on its narrowed pedicle could be increased by mechanical forces (bending or twisting of the body as a whole, or a blow to the abdomen), until amputation occurred. Spontaneous amputation secondary to torsion was observed also by Rokitansky and Praeger.

February 8, 1926.

PRIMARY ACUTE AORTITIS

B. Z. RAPPAPORT

Primary acute aortitis is a rare condition. Only ten cases have been reported (Stumpf: *Ergebn. d. allg. path. u. path. Anat.*, 1913, p. 56). Aortitis secondary to adjacent mediastinal infection or to aortic endocarditis is a more common condition.

A man, aged 47, with a syphilitic infection twenty years previously, and a positive blood Wassermann reaction, was admitted to Dr. Williamson's service at the Illinois Research and Educational Hospital. His complaints were due to cardiac decompensation of eighteen months' duration, worse during the last five weeks. The physical findings were those of cardiac decompensation and an enlarged heart, a systolic murmur over the apex and a diastolic murmur over the sternum. The blood pressure was 175 systolic and 70 diastolic. The temperature was normal. The patient died sixteen days after admission.

The necropsy by Dr. R. H. Jaffé was limited to an abdominal incision. There were recent infarcts of the lungs, hyperemia of the kidneys and the liver, and in the thoracic aorta a syphilitic sclerosis. In addition, there were five or six yellow plaques 2 to 3 mm. in diameter just above the aortic cusps. No changes suggestive of a healed or recent endocarditis were found. The heart was markedly enlarged.

Microscopic examination of the aorta demonstrated the usual tissue changes characteristic of syphilis, and also an acute inflammation. Miliary abscesses composed of polymorphonuclear leukocytes in and about regions of necrosis were present in the media and between the intima and media pushing the former layer toward the aortic lumen. The elastic fibers were destroyed in these places. Gram-positive streptococci and diplococci were found. In some regions hyaline bodies, described as Russel or fuchsin bodies, were present. Cultures of the blood at necropsy contained a green producing streptococcus. The mode of infection was considered hematogenous from a focus not demonstrated by the necropsy. The preexisting syphilitic changes of the aorta were considered the predisposing cause in diminishing the local resistance to infection.

DISCUSSION

Dr. H. G. Wells: When examining sections from cerebral and coronary arteries, the site of fatal thrombosis, I have been impressed with the frequency with which the sclerotic lesions, whether syphilitic or senile, on which the thrombosis has taken place, have shown histologic evidence of acute inflammatory processes. This has suggested to me that the common fatal accident of cerebral and coronary thrombosis is frequently the result of lodgment, in these areas of tissue injury in the arteries, of pathogenic bacteria circulating in the blood. Without such a superimposed infection of the sclerotic patches the thrombosis might not have occurred.

Dr. R. H. Jaffé: I am especially interested in Dr. Well's statement. During and after the great pandemia of influenza in 1918 I made the observation that a relatively large number of middle-aged persons had died suddenly from coronary thrombosis. The changes in the walls of the coronary vessels were slight, and did not exceed those usually found in persons above 45 years of age.

With regard to Dr. Rappaport's case, I should like to say that the chronic syphilitic changes in the media and adventitia of the aorta seemed not to be affected by the acute purulent process in the intima.

February 8, 1926.

SOME MISCONCEPTIONS REGARDING THE RELATION OF HEREDITY TO CANCER AND OTHER DISEASES

STUDIES IN THE INCIDENCE AND INHERITABILITY OF SPONTANEOUS CANCER IN MICE: TWENTY-THIRD REPORT *

MAUD SLYE

A very serious handicap is met in the effort to make known the facts of heredity and to place these facts in their proper relation to other biologic data, for the purpose of establishing the exact value of heredity among the biologic influences, so that we may have a firm basis for further departure, and not be forced continually to replow the same ground. This is particularly true in attempting to establish the relation of heredity to disease.

This serious handicap consists in what may well be called fundamentalism in the scientific field; that is, preconceived ideas and prejudices, not based on scientific research, but instead on general impression, hearsay evidence and the like, handed on from one to another and thus established in general opinion.

Scientific terms, frequently misunderstood and misused by clinicians and research workers, form a strong background of entrenchment to prejudice and preconceived opinion. One of these terms is "eugenics," which has been used to mean anything from personal and social hygiene, and childbirth conditions, prenatal and postnatal, through to the real facts of heredity. These widely divergent usages of the word eugenics have led to a rather widespread confusion among terms as different in meaning as sanitary, congenital and hereditary.

Personal and social hygiene have much to do with good birth, and they do determine those conditions which are congenital. They can in no way determine hereditary characters. They may influence the extent to which hereditary characters can develop, just as conditions of wholly external origin, such as lack of food or lack of sunshine can determine after birth how far certain hereditary characters can develop.

A congenital disease is contracted in utero. Any disease that is hereditary is not so contracted, but

* From the Cancer Laboratory of the Otho S. A. Sprague Memorial Institute and the University of Chicago.

instead is the result of characters derived from ancestral germ plasm, inherent in the ovum and in the sperm cell. By the right line of experimentation, hereditary diseases can be proved not to have been contracted in utero.

This word "congenital" is another of the much misused terms. I am quoting from remarks made at a scientific meeting in a paper whose object was the establishment of one of the "cancer germs" somewhat recently discovered. "The fact that cancer is hereditary has nothing to do with whether or not it is an infection, as we all know that syphilis is hereditary, and syphilis is a specific infection." Such confusion between "congenital" and "hereditary" is not infrequent, and it is destructive of any correct understanding of heredity and the bearing on the etiology of disease which any given type of true inheritance behavior may have.

Intra-uterine influences determine what shall be congenital. Such influences do not determine characters that are hereditary, as these, having been laid down in ancestral germ plasm, can be carried through many generations before their frank emergence. As I have stated in a previous paper,[1] such hereditary recessive characters as the tendency to albinism, the tendency to cancer, and the tendency to the dancing habit shown in the Japanese waltzing mouse, have repeatedly been held back in this laboratory for over twenty-five generations. Submerged beneath a dominant character, they are carried along through generation after generation by hybrid carriers wearing the dominant appearance, but they are always potential in the strain as long as hybrid carriers are bred with the dominant. When eventually two of these hybrid carriers are mated, the next generation will frankly show, in some of the offspring, this recessive character (albinism, cancer, the dancing habit, etc.) which has been submerged in hybrid carriers for any number of generations desired. Such behavior of any character takes it wholly outside the realm of the congenital and places it indisputably among the characters that are hereditary. This test of whether or not a character can be transmitted through generation after generation without its frank emergence should always be made in the study of the inheritability of any recessive character, in order to be certain that it is truly hereditary and not congenital.

1. Slye, Maud: J. Cancer Research, April, 1926.

The question of the inheritability of disease types seems to be of interest both to the medical and to the lay mind. In view of this long continued and very general interest, it is striking how few adequate studies have been attempted in the question of the relation of heredity to any pathologic condition.

In the absence of such studies, it is equally striking how generally an "opinion" is held on the subject of heredity, when the question is raised in connection with any given type of disease. There seems also to be a strong desire to think that diseases have no hereditary basis, and a readiness to accept the opinion that any given disease is not hereditary without any adequate data whatever, whereas the most incontrovertible evidence that any disease is hereditary does not carry conviction to such minds.

For example, at the symposium on rickets held at the 1924 session of the American Medical Association, the unanimous pronouncement was made that rickets is not hereditary "in the true sense" (whatever that expression may mean), and an editorial accepting this pronouncement and rejoicing in it shortly followed in The Journal.

This pronouncement was not the outcome of adequate heredity studies of rickets, but of the opinion of the speakers at the symposium, based presumably on dearth of direct evidence of inheritability in the particular rickets subjects handled in their service.

This illustration is typical of the method commonly in vogue in handling questions of heredity in relation to disease. I desire strongly to reemphasize the misleading nature of such extempore "opinions" on the subject of heredity, since heredity is a most profoundly determining factor in the nature and behavior of any disease, and pronouncements on the subject should be based only on intensive heredity studies.

Thus, the most serious of the obstacles in establishing the facts and influence of heredity is the very general misconception of the nature of heredity itself, and of the type of test that is adequate to prove the inheritability or noninheritability of any disease. One of the fundamentalist views concerning heredity is that if we study the two parents we have canvassed the field. It is therefore a matter of surprise to those who hold this point of view, when two black parent mice have white offspring; or two brown-eyed human parents have blue-eyed children, or two human or mouse parents without cancer have cancerous offspring. To be consistent in

these cases would be to decide that black hair is not inheritable and that brown eye-color is not inheritable, since it is on such a basis that such investigators decide that cancer is not hereditary. Positive conclusions regarding heredity are frequently based on information concerning the parents only. Not infrequently, scientific investigators announce the inheritability of a disease on so inconclusive a test as mating two individuals with the same disease and finding that the immediate offspring also have the disease.

Some better informed statisticians would take the record not only of the two parents but also of the four grandparents, and with entire conviction they base their conclusions concerning heredity on these data. But it is easily possible, in heredity, that there should appear

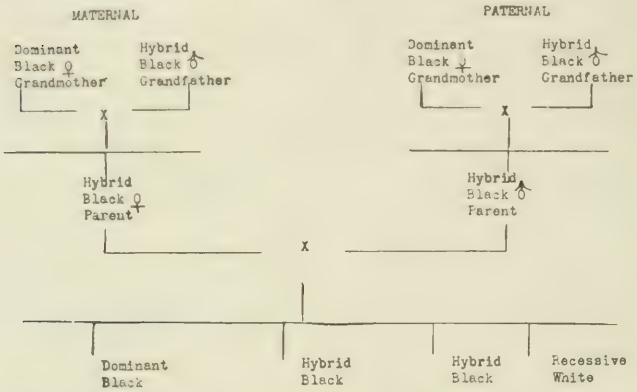


Fig. 1.—How albinos can be derived by the classic method, when neither parent nor any one of the four grandparents was albino.

in the third generation a character shown by neither parent nor any one of the four grandparents, as shown in the accompanying diagrams.

As shown in figure 1, pigmentation is dominant over the lack of pigmentation (albinism). If, therefore, we mate two black mice, one of which is hybrid black (that is, carries albinism potentially) and the other purebreeding black, we shall get only black mice in their immediate offspring. One half of these will be purebreeding black, and one half will be hybrid black, and nothing in their external appearance indicates which are dominant black and which are hybrid black. If then we select for both parents of the next generation hybrid black individuals from such a cross, we shall get some albino mice in the immediate offspring.

Here, then, are albino mice readily obtained from ancestry which showed no white in either parent or any

one of the four grandparents. By mating two of these whites, we shall immediately get a 100 per cent albino strain, which will remain 100 per cent albino, unless pigmentation is again hybridized in. Thus, by one mating of two recessive albinos derived from hybrid black is a strain, which had apparently been 100 per cent black, immediately converted in this branch into 100 per cent white.

As shown in figure 2, again, brown eye-color is dominant over blue eye-color. If we select as grandparents one purebreeding brown-eyed and one hybrid brown-eyed individual for each pair, one half of their immediate offspring in each case will be purebreeding brown-eyed, and one half will be hybrid brown-eyed individuals, and nothing in their external appearance

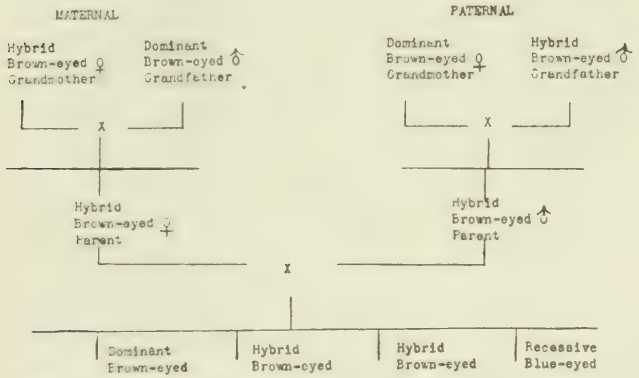


Fig. 2.—How blue-eyed individuals are readily obtained when neither parent, nor any one of the four grandparents, was blue-eyed.

will distinguish the dominant brown-eyed from the hybrid brown-eyed. If two of these hybrid brown-eyed individuals are selected as parents, some of their offspring will be blue-eyed. Indeed, it is possible and frequently occurs that the only offspring born of a hybrid brown-eyed pair (when there are but few children) are blue-eyed.

We have, then, blue-eyed individuals readily obtained when neither parent nor any one of the four grandparents had blue eyes. By mating two such recessive blue-eyed individuals, we shall in one generation convert into a 100 per cent blue-eyed family what had until this mating apparently been a 100 per cent brown-eyed family, since double recessive parentage gives 100 per cent extracted recessive young.

In exactly this way, since cancer susceptibility seems to be recessive to cancer resistance, it is possible to get in the third generation cancerous individuals in which

neither parent nor any one of the four grandparents was cancerous, but in which each parent was hybrid noncancerous, while in each pair of grandparents one individual was purebreeding noncancerous, and one was hybrid noncancerous, as shown in figure 3.

Here, then, are cancerous individuals readily obtained, of which neither parent nor any one of the four grandparents had cancer. By mating two of these recessive cancerous individuals, we shall in one generation convert into a 100 per cent extracted cancer strain what until this mating had apparently been a 100 per cent noncancerous family.

In the same way, that is, by the continued mating of purebreeding black with hybrid black, it would be possible to prevent the appearance of white for twenty-five generations, or for fifty or as many generations

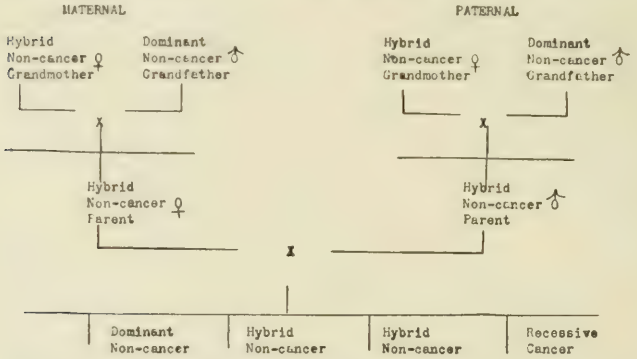


Fig. 3.—How cancerous individuals can be obtained by the classic method, when neither parent nor any one of the four grandparents had cancer.

as is desired. As long as one parent in each pair is purebreeding black, no white will occur in the offspring. As long as one of the parents in each pair is hybrid black, white will be carried potentially in the strain. This can be done for any number of generations desired. But when, in any generation, both of the parents selected are hybrid black, white offspring will appear.

In the same way blue eyes can be kept out of the family, but will remain in it potentially as long as purebreeding brown-eyed individuals are mated with hybrid brown-eyed. But when two hybrid brown-eyed individuals are mated, blue eyes will appear in their immediate offspring.

In exactly this way, I have found that as long as one parent is a pure-breeding cancer-resistant individual, no cancer will appear in the offspring. As long as one

parent is a hybrid cancer-resistant individual, cancer susceptibility will inevitably be carried potentially in the family, through the hybrid cancer-resistant individuals, for any number of generations. When finally two hybrid cancer-resistant individuals are mated, some of their immediate offspring will be cancer susceptible. That is, in every character transmitted by heredity, cancer or any other character, whatever its nature may be, as long as a purebreeding dominant is mated with a hybrid carrier, the recessive character will not appear, but will certainly be transmitted through the hybrid carrier for any number of generations, while the mating is of this type. When eventually two hybrid carriers are mated, the recessive character will appear in some of the immediate offspring. In the chance matings of the human species, the mating of two hybrid carriers of any given recessive (like cancer) is almost certain to occur sooner or later. When it does, the recessive character appears in some of the children. This accounts for the sudden appearance of cancer sometimes in human families in which there has been no known cancer for two or more generations.

When these facts of heredity are grasped, there is at once apparent the absurdity of attempting to settle the question of the inheritability of any character whatever by the statistical method. For while the statistician, endeavoring to settle the question of the inheritability of any disease, can perhaps get the death facts and the life facts of both parents and possibly of the four grandparents, and perhaps eventually even of all the great grandparents, he cannot discover which of these individuals are purebreeding resistant to cancer (or any other disease), and which are hybrid cancer-resistant, for there is no way to discover this fact except by the experimental method of selective breeding and analysis with the right number and the right kind of hybrid crosses.

Only by the experimental analytic method can the question of the inheritability of any character whatever be settled definitely. Prevailing monogamy in any species makes analyses very difficult.

EXPERIMENTALLY PRODUCED CANCER

In discussing the bearing of studies in experimentally produced cancer on the question of cancer heredity, let us briefly review the history of the fundamentalist reception of the demonstrated fact of the inheritability of cancer, and the facts of the experimental production of cancer.

When these studies in spontaneous animal cancer were first published in 1911, practically all other studies in animal cancer were being carried on with grafted tumors. It had been demonstrated [2] that the inheritance behavior of grafted tumors indicated multiple factors, paramount among which was a dominant, determining a successful "take" of grafted cancer in the first hybrid generation.

The fact that studies in this laboratory demonstrated the inheritance behavior of spontaneous cancer to be that of a simple mendelian recessive caused the fundamentalists to think that geneticists did not agree as to the behavior of cancer heredity. They therefore discarded the entire fact of the inheritability of cancer. As I have stated in a previous article,[3] the findings in these two lines of studies are in perfect harmony, since a "take" of grafted tumor depends on the normal regeneration of the host tissues, and a spontaneous cancer depends on the abnormal regeneration of the tissues. Both studies, then, demonstrate the dominance of normal regeneration over abnormal regeneration. And there is therefore not even disharmony in regard to the method of the inheritability of cancer for the fundamentalist to base his objections on.

Next in history come the so-called "spiroptera cancers" of Fibiger's work,[4] which were immediately taken by the fundamentalist as a proof that cancer could be experimentally produced in all subjects, and therefore was not inheritable, entirely disregarding the demonstrated inheritance behavior of cancer in every test made by every student of the subject. Fibiger's work, carried outside the inbred strain of rats in his own laboratory to wild Norway rats, other strains of laboratory rats and strains of mice, showed that spiroptera cancer was not produced in all subjects.

The results of his studies are thus in perfect harmony with heredity studies in grafted cancer and in spontaneous cancer; that is, spiroptera cancers were produced only in susceptible members of susceptible strains of susceptible races. The finished results of Fibiger's study of spiroptera cancer therefore left no ground for scientific opposition to the fact of the inheritability of cancer.

Bullock and Curtis' studies [5] in liver sarcoma in rats, following experimental feeding with tapeworm larvae, fall into the same class with Fibiger's results; that is,

2. Tyzzer, E. E.: J. Med. Research **16**: 519, 1909; J. Cancer Research **1**: 125 (April) 1916. Little, S. W.: J. Cancer Research **6**: 106, 1921.
3. Slye, Maud: J. Cancer Research **8**: 240 (July) 1924.
4. Fibiger: Det. Klg. Danske. selskab. Biol. Med. **1**: 11, 1918.
5. Bullock, F. D., and Curtis, M. R.: J. Cancer Research **8**: 1 (April) 1924.

they also demonstrate dependence on hereditary predisposition for success in the experimental production of these tumors.

Next followed the tar cancers, first produced by Yamagiwa in rabbits, and now widely studied in rats and mice by perhaps the majority of the present day workers in animal cancer research.

It is too early as yet to say what the final residuum will be from the study of tar cancers, since so many of these studies are still under way. But whether or not it is eventually found that tar cancer can be produced in all subjects, the conclusion cannot decide the question of the inheritability of cancer, and must be in agreement with all other facts of cancer, one of which is its demonstrated inheritability.

No one can deny the inheritability of the tendency to grow hair, yet continued painting with sufficiently strong coal tar products destroys the hair-growing mechanism. In all probability, continued painting with sufficiently strong coal tar will destroy every inherited tissue and every inherited function of the body. That is, no tissue, no function and no tendency of the body is immune from destruction. Coal tar products of sufficient concentration are very destructive agents and undoubtedly can destroy the cancer-resisting mechanism.

Thus the method used in the experimental production of unions may be destroying the very tendency it attempts to test. Therefore, the question of the inheritability of cancer resistance cannot be settled by determining whether cancer can or cannot be experimentally produced by any given method in any given set of subjects, since there is not and cannot be any complete biologic control in the field of heredity in such studies, nor any certainty that it is only the inheritability of the tendency to cancer resistance which is being tested in such experimentation.

PUBLIC PROPAGANDA

Another type of obstacle in establishing the facts of cancer heredity is the extraordinary idea apparently prevailing in some minds that since human heredity cannot at present be controlled, because we cannot control and experiment with human matings, the demonstrated facts of heredity do not apply to the human species and may therefore be categorically dismissed. For example, note the statement recently made by Wood of the Columbia Institute of Cancer Research:[6]

6. Wood, F. C., in discussion on cancer, J. A. M. A. **85**: 1050 (Oct. 3) 1925.

Of course, the animal experimentation done by Maud Slye in Chicago and by Bullock and Curtis in my laboratory have definitely proved that in animals a susceptibility to cancer is transmissible. Of that there can be no question. The breeding experiments, however, are so complicated and take so long that if they were applied to human beings it would mean that for the last 5,000 years both parents of these unfortunate human beings would have had to have cancer. That is a concentration of breeding which cannot occur in the human race. So the facts of the high incidence of cancer in their experimental studies cannot be applied in full value to human beings.

This idea, that to test the inheritability of cancer in man would take 5,000 years, with double cancerous parentage in each generation, has no scientific basis whatever. The second argument is equally untenable, for Wood says in effect that the fact that we cannot make a 5,000 year test of the inheritability of human cancer warrants us in discarding the facts of cancer heredity so far as man is concerned.

An answer[7] to this statement appeared in THE JOURNAL, part of which is repeated here.

The 100 per cent cancer strains that have been produced in any laboratory have been produced from a double cancerous parentage somewhere in the line. But this does not mean that there must have been a series of double cancerous parentage for any length of time corresponding to anything like 5,000 years of human heredity, or even for more than one generation. *One generation of double cancerous parentage will produce 100 per cent cancer susceptible offspring,* exactly as double albino parentage for only one generation will produce 100 per cent albino offspring.

The long series of many generations of 100 per cent cancer have been charted, not because countless generations were necessary to produce them, but to demonstrate that they actually were 100 per cent cancer strains and continued so for as many generations as we continued a double cancerous parentage. It is not alone these strains of double cancerous parentage which prove the inheritability of cancer, but still more potent in this proof is the behavior of cancer in hybridization.

Only two generations of exact facts are necessary to demonstrate inheritance behavior where the cross is between a cancerous individual and a noncancerous individual who is not a cancer carrier. Three generations of exact facts—not of double cancerous parentage—are necessary to determine how cancer behaves in heredity when a hybrid carrier is mated with a cancerous individual, or with a noncancerous individual

7. Slye, Maud: Cancer Heredity, J. A. M. A. **85**: 1242 (Oct. 17) 1925.

that is not a cancer carrier. This is true in mice, in man or in any other animal, or in any plant.

The difficulty in studying human heredity is not that we cannot have double cancerous parentage, or any other type of double parentage for 5,000 years, but that we cannot get the exact facts for even one generation. It is because of this lack of exact facts and because we cannot experiment on human beings in this and many other lines that we must get our exact facts from animal experimentation.

That we are justified in applying these facts, where they are basic biologic facts, is one of the best assets derived from the discovery of the fact of evolution.

I bring up the quotation from Wood again at this time because it represents the type of reasoning that has governed the pronouncements on the subject of cancer heredity, in the publications of the American Society for Cancer Control. These publications in their turn have annually governed the propaganda concerning cancer heredity, in the various cancer control meetings all over the United States, and they are, moreover, quoted abroad. Thus easily does the fundamentalist doctrine spread.

In no other field of scientific endeavor do we assume that, because at present we cannot make a particular test of a demonstrated scientific fact (such as controlling human matings), therefore it is not a fact and we can forthwith discard it, nor do we discard the conclusions of higher mathematics and of higher physics because they are complicated.

The great difficulty in the study of human heredity is that man is so long lived an animal that no one person can collect accurate data for three generations. But this does not mean that there are no heredity facts unbrokenly expressing themselves in the human species just as they do in other animals of a shorter life span, whose exact records are being taken. If we should establish permanent records of periodic examinations of each living individual and permanent recorded accurate necropsy findings of all dead, in three generations we should have valuable scientific data. These data would undoubtedly include matings of double cancerous parentage, matings of double noncancerous parentage, matings of noncancer with hybrid carrier, and matings of cancer with hybrid carrier. These are exactly the matings by which we test the inheritability of cancer in short lived animals, and such records, if accurately taken and correctly interpreted would furnish an equally exact test for the human species.

STRAINS SUPPOSED TO CARRY A FIXED CANCER PERCENTAGE

Another strong obstacle in the way of establishing a clear comprehension of the relation of heredity to cancer is the announcement by workers in heredity, and by other workers in medical research, of what they designate as strains of animals carrying a permanently fixed percentage of any given character, as, for example, cancer.

The literature has several instances of the announcement of strains carrying a fixed percentage of cancer, to which it is perhaps unnecessary to make reference here, except when the assumption of a fixed percentage of cancer within a strain has been taken as the single basis for further research, as in the recent work of Lynch [8] of the Rockefeller Institute and of Bagg [9] of Cornell Medical College.

The widespread use of tar cancers in current research and the marked success in obtaining high percentages of such proliferations have again strengthened in the fundamentalist mind the idea that cancer is not inheritable, irrespective of the fact of its demonstrated inheritability. This idea has urged on workers in cancer heredity the necessity of demonstrating the relation of tar cancer to cancer inheritance, and Lynch of the Rockefeller Institute has attempted to do this, using materials that were entirely unfitted for the problem involved.

Lynch used two strains of mice, one of which she designates as carrying a fixed high percentage of spontaneous mammary gland cancer, 65 per cent in bred females and 20 per cent in unbred females; and the other, as carrying a fixed low percentage of spontaneous mammary gland cancer, 28 per cent in bred females, and 4 per cent in unbred females. Her object was to determine whether or not painting with tar the skin of mice from these two strains would change the incidence of cancer within the strains, and whether the so-called high per cent cancer strain would show a greater increase in cancers than the so-called low per cent cancer strain.

As Lynch herself very aptly states, "To test the influence of heredity on the response of the skin to tar painting, it would be best to employ strains of animals exhibiting differences in the incidence of spontaneous cancer of the skin."

Not only would it be best in such a test to use as a basis of experimentation susceptibility to skin carci-

8. Lynch, Clara J.: J. Exper. Med. **42**: 829 (Dec.) 1925.
9. Bagg: J. Cancer Research **9**: 498, 1925.

noma, but it is futile to use anything else, since the tendency to other types and locations of neoplasms, such as mammary gland carcinoma, has no influence on the production of spontaneous skin cancer. Lynch's experiments, therefore, have no bearing on the problem attacked. Moreover, having designated her strains as 20 per cent and 4 per cent, respectively, of spontaneous mammary gland carcinoma in unbred females (thereby carefully distinguishing between the cancer rate in bred and in unbred females), she proceeds to use in the experiment, as she says, "approximately one-half males" *whose susceptibility to cancer of any kind has in no way been expressed.* She does not state the age of the mice used, although the average age for the appearance of skin carcinoma differs markedly from the average age for the appearance of mammary gland carcinoma, and the matter of age differences should be under careful control in such an experiment.

But the gravest objection to experiments of this kind is the assumption of fixed percentages of cancer within a strain that is not homozygous in regard to cancer. It is wholly unscientific to assume fixed percentages of any character within such a strain on the basis that, to date by the matings made, it has yielded such a percentage of the given character. The past history of cancer production within a heterozygous strain cannot scientifically be assumed as the certain future history of cancer within that strain, nor can it be taken as the criterion for the cancer behavior of any individual member of the strain, not subjected to analysis.

Every strain that is producing some cancerous and some noncancerous individuals is heterozygous to cancer, just as every strain that is producing some black and some white individuals is heterozygous to albinism. Every noncancerous member of a heterozygous cancer strain is heterozygous to cancer unless at least one parent of that individual was dominant noncancerous, and one half of those with one dominant noncancerous parent will be heterozygous to cancer, since the mating of a dominant with a hybrid carrier produces one-half dominant and one-half hybrid carrier. Any strain that has to date yielded 4, 20, 28 or 65 per cent of cancer, like Lynch's strains, is heterozygous to cancer, and the cancer potentiality of every one of its members is dependent wholly on what matings have been made, just as its future cancer percentage will depend on what matings may be made. In addition to its cancerous members, such a strain is made up of some dominant noncancerous members and some hybrid car-

riers, and nothing in the external appearance will distinguish between the latter two types.

As I have already pointed out in this paper, recessive characters, such as the tendencies to albinism, to blue eyes and to cancer, which are submerged in hybrid carriers wearing the dominant appearance, can be made to appear suddenly within a strain, by the mating of two hybrid carriers. It is thus shown to be possible to convert, by two matings, a strain heretofore always wearing 100 per cent of the dominant appearance into a strain expressing 100 per cent of the recessive.

We cannot scientifically say that any heterozygous strain inherently carries a fixed percentage of cancer. We can only say that during the life of the strain, it did, under the matings made and the handling given it, produce a certain percentage of cancer. We must at the same time admit that, with different types of matings and different handling, the same strains would have produced wholly different percentages of cancer. The very foundation, therefore, on which Lynch's entire experiment is based vanishes away. The problem can never be scientifically attacked by this method.

The work of Bagg of Cornell Medical College, reported at the 1925 meeting of the American Society for Cancer Research, is open to a similar basic criticism. Bagg's experiments were designed to test the relation between functional disturbances of the breast to the incidence of mammary carcinoma in mice. He says that "a carefully inbred strain of animals with a well known low rate of tumor incidence was selected." He does not state what this low rate was. The control group of mice showed an incidence of 5 per cent of breast carcinoma. These mice, he says, "were breeding normally; that is, the females were remated only after nursing their litters for about six weeks." Of course this method is in miniature the method of human breeding and it does not necessarily define normal breeding in mice. The group of fifteen mice subjected to various types of experimental dysfunction of the breast showed an incidence of 85 per cent of breast carcinoma.

I do not find any suggestion by Bagg that his results had any bearing whatever on the question of the inheritability of cancer, or that they were intended to have such a bearing. The fact of the inheritability of cancer, however, has a marked bearing on his experiments. It must be that he recognized the necessity of taking advantage of cancer susceptibility, since he very wisely selected a strain that was yielding carcinoma of the breast. Had he sought results opposed to the fact of

cancer heredity, he should have made his tests on a strain that was analyzed cancer free, and should have secured complete biologic control in every other element of his experiment.

His experiments, then, were apparently designed to test the relation of experimentally produced breast trauma to breast carcinoma, in strains predisposed to breast cancer. In this selected strain, predisposed by heredity to breast carcinoma, he found a greatly higher incidence of breast cancer in the individuals that he had selected for experimental breast trauma.

There are two pertinent suggestions to be made here:

1. As I pointed out in my discussion of Lynch's work with tar cancers, it is unscientific to assume a fixed percentage of cancer in strains heterozygous to cancer. The fact that a strain, under the matings made, has yielded a given percentage of cancer, for example, as in Bagg's control group 5 per cent, cannot be taken as the criterion for the future production of tumor in that strain, or the percentage of tumor production in any other group of any other individuals in that strain, unless every individual involved has been analyzed and his cancer potentiality has been definitely established.

Bagg's conclusion, therefore, that the 85 per cent breast cancer incidence in his experimental group was due wholly to experimental procedures lacks the same scientific basis lacking in Lynch's work. It is easily possible in a strain which to date has never yielded more than 5 per cent of breast cancer to secure suddenly 100 per cent of breast cancer by the right selective matings, or 85 per cent. It is not impossible that the fifteen mice selected for his experimental group were exactly the ones which under any handling would have produced breast cancer; and such a possibility should be ruled out by complete biologic control.

Any strain which to date has produced 5 per cent or 85 per cent of cancer, like Bagg's strains, is heterozygous to cancer, and no assumptions are warranted as to the cancer potentiality of any unanalyzed groups or individual members of the strain. Moreover, in all such experiments, these should be recognized the source of error, even in individuals examined at necropsy, of deaths from intercurrent disease that prevents cancer development.

I have for years been urging on research workers the necessity of using biologically analyzed stock for their experiments, instead of assuming that results secured on unanalyzed stocks are wholly due to experimental procedures.

2. So far as I know, there is no worker in cancer research today who does not recognize the necessity

of stimulations, irritations or traumas, either minute or gross, as a basis for cancerous growth. The fact that various types of irritations play an important part in the causation of cancer in susceptible individuals is one of the best basic arguments for defining cancer as an abnormal regenerative process. This regeneration after trauma apparently is abnormal in these cancer susceptible subjects, because of the lack of a differentiating mechanism in the tissues. It seems to be this local lack of a differentiating mechanism in susceptible tissues that is the hereditary element in cancer susceptibility. That is, the type of local response made to a given type of irritation is determined by heredity, whatever the type of that irritation may be.

If Bagg had worked with individuals every one of which was analyzed as to its cancer potentiality, if he had selected groups exactly homologous in the matter of cancer potentiality, individual for individual, and with such groups of homologous individuals and with numbers large enough to make a test had obtained just such results as he did obtain in his experiment, he would have given us a scientific demonstration of the relation of these particular types of trauma to breast cancer causation in his tested strains. Such conditions would have constituted a complete biologic control for those particular groups of animals.

It is very easy to assume after any particular experimental procedures that the end-results are wholly caused by such procedures; but if animals are used which have not been analyzed in the potentiality being tested, there is no basis for such an assumption.

In this connection, it might be of interest to mention mouse 21663 of this stock. She was picked up when 2 weeks old, with two carcinomas of the mammary gland, 10 and 3 mm., respectively, in diameter. She lived one week more, and at necropsy and on histologic examination, proved to have two carcinomas of the mammary gland, bilateral kidney sarcomas (the left kidney almost entirely destroyed), and osteosarcomas of the fifth rib and of the spinal column. Needless to say, this mouse had not been mated, nor had her ovaries been experimented on by removal or otherwise. But she was the great granddaughter of female 12058 with sarcoma of the kidney, bilateral sarcoma of the uterus and bilateral sarcomas of the ovaries. She was the granddaughter, five generations removed, of female 26 with sarcomas of the kidney, ovary, liver and mesentery. She was the granddaughter, eight generations removed, of female 3 with a sarcoma-carcinoma of the mammary gland, a malignant adenoma of the liver and sarcoma metastases in the kidney, in a strain which was being

deliberately bred for kidney and liver tumors, and in her ancestry there was considerable percentage of osteosarcomas. It is also of interest to note that exactly the types of so-called functional disturbance used in Bagg's tests in his groups 1 and 2, that is, early and constant breeding of young females with removal of the young immediately after birth, have in this laboratory never occasioned mammary gland carcinoma in analyzed individuals of analyzed cancer free strains.

Although Bagg himself did not assert that his results had any bearing on the fact of the inheritability of cancer, in the discussion of his paper Ewing [10] of Cornell Medical College took occasion to say: "Carcinoma has been developed in a strain of animals which had very little natural tendency to develop the disease. If there had been any congenital or hereditary characters in the development of these carcinomas, it does not appear in these experiments of Bagg's. He has watched this group of animals for thirteen years and has found a very low incidence of cancer, so I think that these experiments offer a somewhat difficult problem to those who believe in the congenital or hereditary incidence of cancer."

So far as I know, no research worker who has made any study of the incidence of cancer defines it as a congenital disease, so we may dismiss that portion of Ewing's remarks. Moreover, the inheritability of cancer is no longer a matter of belief, but it is a matter of exact demonstration.

Evidently, Ewing did not see the paradox in his first two sentences. For in the first he admits the strain used had a little natural tendency to carcinoma of the breast; while in the second, he says that no hereditary character in the development of the disease appeared in the experiment.

As I have stated, a strain which to date has been producing 5 per cent breast cancer can in one mating be changed to a wholly different percentage of breast cancer, and any experimental procedure which assumes the continuation of a fixed percentage of cancer in unanalyzed strains is based on assumption only.

Loeb [11] also, in attempting to demonstrate the relation of the ovaries to breast cancer incidence, used what he called "a strain of mice with a known high tumor incidence," and concluded from his experimental procedures that removal of the ovaries lowered the incidence of tumor within the strain.

As I have repeatedly stated since the first publication of this work fifteen years ago, the type of product within a

10. Ewing, James: J. Cancer Research **9**: 500 (Dec.) 1925.
11. Loeb, L.: J. Cancer Research **1**: 1 (Jan.) 1916.

strain depends on the matings within that strain, just as certainly as the type of chemical result depends on what chemical combinations are made. If we combine zinc with sulphuric acid we shall get one kind of result; if we combine it with hydrochloric acid we shall get a different result. In just this way and just as surely, if we mate an albino with a red mouse, we shall get one type of offspring; if we mate the same albino with a gray mouse, we shall get a different type of offspring. If we mate the same gray mouse with a first generation albino derived from red (and hence a hybrid carrier of red), we shall get entirely different results; that is, some red, in the first hybrid generation.

Any strain can in one mating be changed in the percentage it carries of any inheritable character, including cancer, according to the mating made. The greatest caution, therefore, will be necessary to secure complete biologic control, in any effort to discover the relation which experimental procedures of any kind may bear to the causation of cancers of any type or any location, or the relation of the basic facts of cancer heredity to such results. The assumption that fixed percentages of cancer can permanently define a heterozygous strain, or any group or any individual members of such a strain, will certainly have to be excluded.

We shall never get the right idea of heredity, and hence we shall never work out correctly the facts of inheritance and its complex and intricate influences throughout all organic response to every type of test, until we conceive of strains as plastic in every generation, susceptible of being changed by one mating of the right kind from 100 per cent of a character to zero per cent of that character, or to 50 per cent, and susceptible of being changed by a series of matings to any percentage desired. If this were not true, and if strains were fixed in the percentage they carried of any inheritable character, there would be no such thing as heredity, since the new hybrid mating would bring nothing to the strain; that is, the new individual would have no inheritance to offer.

ALL FACTS OF CANCER MUST BE CONSISTENT EACH WITH THE OTHERS

In the diverse lines of approach used by the many workers in any field of scientific research, there are sure to be made evident gaps in our knowledge. But these gaps do not entitle us to deny a scientifically demonstrated fact, because we cannot yet in our own minds make it accord with our own particular discovery or our own particular theory.

As in any other field of scientific endeavor, all the facts in the field of cancer research must be consistent each with every other. If it should eventually be possible to produce experimental cancer in every subject, this would not disprove the inheritability of cancer any more than the fact of the inheritability of cancer proves that it must be impossible to produce cancer experimentally in every subject. No biologist has ever made such an assertion. There must instead be a third fact that harmonizes these two. This third fact is already evident in the highly destructive nature of the experimental agents used, which may well destroy the cancer resistant mechanism or any other bodily mechanism. Spontaneous cancers do not arise in every individual, either in the human species or in lower animals even under identical conditions; this is a demonstration that there is a cancer resistant mechanism present in some members of every species. No amount of experimentally produced tumor can offset this fact. The explanation of these tumors will have to harmonize with it.

Again, if cancer should eventually be demonstrated to be a specific infection, this would not disprove its inheritability any more than the fact that the inheritability of cancer definitely proves that cancer is not a specific infection. There must be a third fact that would harmonize these two. That third fact is readily discerned even now in the hereditary basis of every organic response to every type of stimulation or irritation, whether it is a specific germ or anything else, although there is variation in the types of inheritance behavior, and apparently these variations have a bearing on the etiology of various diseases.

The third most frequent objection to the inheritability of cancer, namely, that although proved for lower mammals it does not apply to man, is answered by the fact of evolution. Similar tissues derived in the course of evolution from the same ancestry must respond in the same way as the ancestral tissues to the same types of stimulation. Only so could an unbroken series of organisms evolve each from the other.

The scientific method of procedure for those who cannot accept the evolutionary evidence is not categorically to deny what they cannot disprove and what has indisputably been found true by many workers, but rather to begin the measures which inevitably must produce scientific data for the investigation of heredity in man.

March 8, 1926.

THE NATURE OF THE ACTIVE PRINCIPLE IN TUBERCULIN

ESMOND R. LONG
AND
FLORENCE B. SEIBERT

Tuberculin may be defined as a preparation obtained from the tubercle bacillus, which elicits a specific inflammatory response in tuberculous animals, but is nontoxic for normal animals. Many different kinds of tuberculins are available, which presumably owe their activity to an active substance common to all.

The nature of this active substance has been frequently but not exhaustively investigated. The problem is a fundamental one, not only for its bearing on tuberculosis, but also for its bearing on other chronic infections. Presumably such reactions as the luetin, mallein and abortin reactions are identical in character, and the agent responsible for the reaction of hypersensitiveness belongs to the same chemical fraction of the infecting micro-organism in each case.

Argument has rested chiefly on the question whether the active principle of tuberculin is a protein or not. To aid in the solution of this problem we have carried out the following experiments: Tuberculin was prepared in large quantity from a medium of the following composition: asparagin 5, ammonium citrate 5, potassium acid phosphate 3, sodium carbonate (dry) 3, sodium chloride 2, magnesium sulphate 1, ferric ammonium citrate 0.05, glycerol 50 and water 1,000. The tubercle bacillus grows luxuriantly on this medium, yielding a highly potent tuberculin which invariably contains protein.

The activity of preparations made from the growth of tubercle bacilli appears to be due to a colloidal substance, for as a rule on prolonged dialysis no active substance passes through the dialyzing sac, even when all the salts, color, odoriferous substance, glycerol and other constituents of the original medium have dialyzed out. Occasionally small amounts of active substance appear to diffuse, particularly after much chemical manipulation of the material.

The methods of protein precipitation throw active substance out of solution. Acetic acid precipitates a protein which is active, maximum precipitation occurring at p_H 4. Precipitation is not complete, however. The filtrate still contains protein and still has tuberculin activity. Trichloracetic acid precipitates protein more nearly completely; however, traces of protein and at the same time of active substance remain in solution. Saturation with ammonium sulphate precipitates at the same time all of the protein and all of the active principle.

On hydrolysis of tuberculin, whether by enzymes or by acid, activity remains as long as protein of the type classed as whole protein is present. We have selected precipitation by trichloracetic acid as an arbitrary measure for whole protein. As protein decreases and proteose increases in enzymic digestion, activity decreases. When proteose alone is destroyed by erepsin, the activity of the preparation is not affected. The protein which can be precipitated by

trichloracetic acid from tuberculin exposed to mild acid hydrolysis is highly active, but a small amount of activity persists in the proteose fraction after the removal of the trichloracetic acid precipitate.

From these experiments it seems probable that the activity of tuberculin is associated primarily with a protein molecule, but persists in spite of a certain amount of disintegration of the molecule.

March 8, 1926.

MUTATION FORMS OF THE TUBERCLE BACILLUS *

H. C. SWEANY

My attention was first directed to this subject during the course of experimentation on the effect of "Sanocrysin" on the tubercle bacillus.[1] It was observed that, after a certain time of exposure of apparently pure cultures of tubercle bacilli, various forms of organisms appeared that resembled the tubercle bacillus except they were not acid fast. Furthermore, these organisms were gram negative, motile and grew rapidly. An injection into guinea-pigs caused a peculiar type of pathologic change, that will be reported later.[2] At first, these organisms were discarded as ordinary contaminations and the work was repeated, other cultures being used, but with the same results. We observed further that besides the "gold" treatment (which consists in suspending a 5 per cent emulsion of bacilli in 1 : 2,000 "Sanocrysin"), there were other ways of bringing about the same result. One was to grind the organisms in a ball mill for from six to eighteen hours and plant the residue in dextrose bouillon. Another method was to plant them on various mediums that are unfavorable for growth, such as inulin, dulcite and mannite bouillons. In such mediums, it was found that the bacilli had to be planted as a plaque on the surface and had to grow before any unusual forms appeared. After from three to four weeks, many cultures will produce various non-acid-fast forms, while nothing would grow at the time the cultures were planted.

Finally, to check the experiments, we obtained cultures from other laboratories and obtained similar results. Strains H 37 and R 1 were obtained from Dr. Gardner of Saranac, N. Y., and "no. 434" from Dr.

---

* From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium.

1. Sweany, H. C., and Wasick, M. M.: Am. Rev. Tuberc. **12**: 316 (Dec.) 1925.

2. Sweany, H. C., and Evanoff, M.: Am. Rev. Tuberc., to be published.

McCoy of the Hygienic Laboratory. The growth from R 1 was different from the other two in that the rapidly growing form resembled the rather peculiar morphology found in the acid-fast form and did not grow beyond the fourth transplant (fig. 1). This appeared to be sufficient evidence for a thorough study of the problem.

REVIEW OF LITERATURE

Perhaps the first suggestion to variation of the tubercle bacillus was made by Mallassez and Vigual,[3] in 1883 and 1884, shortly after Koch's discovery of the tubercle bacillus. They described what they called "zooglear forms" of tubercle bacilli, because they found zooglear masses, cocci and diplococci in tubercles in which it did not seem possible to them that anything else but a tuberculous virus could be. They reported that these forms were capable of passing over into acid-fast forms. Ferran,[4] first in 1897 and at various times subsequently, described a method of producing a non-acid-fast organism from the tubercle bacillus by reducing gradually the peptone, then the glycerin and sugar in the bouillon culture medium, and eventually obtaining an organism that resembled the typhoid bacillus. By injection into animals, he first obtained an atypical tuberculosis, but he states that by continued passage he has recovered typical Koch forms. This led him to propose the "ubiquity" hypothesis that has been accepted by only a very few others. This hypothesis states, essentially, that the pathogenic forms of tubercle bacilli represent only a small branch of a group of organisms that are found widely distributed in nature and will become pathogenic when they become associated in the animal body. Arloing,[5] in 1898, and Arloing and Courmont,[6] in 1900, reported that they were able to transform the human bacillus into a form like the avian tubercle bacillus. They did this by growing the organism on a glycerin water potato medium and, when a growth appeared, transplanting it to a glycerin bouillon followed by frequent shaking. Dubard,[7] in 1898, obtained similar results. Auclair,[8] in 1903, using a glycerin bouillon, also obtained a non-

3. Mallassez, L., and Vigual, W.: Arch. physiol. norm. et path. **2**: 369, 1883; **4**: 81, 1884.

4. Ferran, J.: Compt. rend. Acad. d. sc. **125**: 515-518, 1897; Arch. de méd. exper. **15**: 753-762, 1903.

5. Arloing, S.: Compt. rend. Acad. d. sc., May 9, 1898.

6. Arloing, S., and Courmont, P.: Cong. internat. de méd., Paris, Sect. de bact. et parasitol. **3**: 178-179, 1900.

7. Dubard, M.: Compt. rend. Soc. de biol. **50**: 474, 1898.

8. Auclair, J.: Arch. Int. méd. expér. et d'anat. path. **15**: 469-88, 1903.

acid-fast organism, but he was unable to regenerate tubercle bacilli from these organisms. Maher,[9] in 1904, described a peculiar behavior of a very large bacillus obtained from barn scrapings, with which he states he was able to produce a tuberculosis in guinea-pigs and which passed through several cycles from the original to an acid-fast granular form. These granules were capable of forming cocci, diplococci and tetrads, and by a special technic, he was able to regenerate acid-fast forms. In a guinea-pig's spleen, he observed orange granules that he thinks are forerunners of these cocci.

About this time, Spengler [10] described what he called "the splitter"—a granular form that occurred in certain strains, more especially in the bovine types. Much,[11] in 1907, described granules of tubercle bacilli that were different from Spengler's by being non-acid-fast, and gram positive, and capable of returning to the acid-fast form. In 1913, Wherry [12] reported the decrease of acid fastness of tubercle bacilli by growing them on a special unfavorable medium. Sivori,[13] in 1920, stated that resistant soil transforms tubercle bacilli into saprophytes, and cited experimental proof. Kolle, Schlossberger and Pfannenstiel,[14] in 1921, attacked the problem, not from mutation but from the standpoint of regeneration of various strains of paratubercle bacilli into true Koch bacilli, and reported a measure of success after several passages through guinea-pigs. Quite recently, Zlatogoroff and his co-workers [15] have attempted to transform saprophytes into true tubercle bacilli but concluded that the question is still open. Pla,[16] in 1924 proposed a theory that is interesting in this connection, principally because he considers coccoid forms (not granular forms only) of organisms present in tuberculous lesions as a stage in the development of true tubercle bacilli and not mutation forms.

In 1924, Karwacki [17] examined thirty-three pleural fluids and reported a variety of cocci and diphtheroid organisms coming from acid-fast bacilli that he does not hesitate to call mutants; he states that the changes are brought about by the difference in lipase and antibody

---

9. Maher, S. J.: M. Rec. **66**: 401, 1904.
10. Spengler, C.: Ztschr. f. Hyg. u. Infectionskrankh. **49**: 541-44, 1905.
11. Much, H.: Beitr. z. Klin. d. Tubrk. **8**: 85, 1907.
12. Wherry: J. Infect. Dis. **13**: 144, 1913.
13. Sivori, L.: Riforma Med. **36**: 1154 (Dec. 11) 1920.
14. Kolle, W.; Schlossberger, H., and Pfannenstiel, W.: Deutsche med. Wchnschr. **47**: 437 (April 21) 1921.
15. Zlatogoroff, S.; Zechnowitzer, M., and Koschkin, M.. Ztschr. f. Hyg. u. Infectionskrankh. **105**: 583, 1926.
16. Pla y Armengol, R., and Fernandez, J. C.: La clinica, November, 1924.
17. Karwacki, L.: Compt. rend. Soc. de biol. **92**: 374 (Feb. 13) 1925; **92**: 801 (March 20) 1925.

content of the respective fluids. He obtained no growth, pure acid-fast organisms in some, and cocci, diphtheroids and spore-forming organisms in others.

In 1925, Pinner and I[18] reported a pathogenic *B. subtilis* associated in tuberculosis. There was also a *B. coli*-like organism disseminated throughout the body not unlike Ferran's organism, although no proof or suggestion was offered at the time that these were related to the tubercle bacillus. Yet it is worthy of passing note. Recently, Stockwell,[19] following up Maher's work, has reported rapid growing, motile, gram-negative bacilli from many cultures examined.

Various experimentors, however, have contested much of this work. Ramond and Ravant [20] were unable to duplicate Ferran's work in any of its aspects. Calmette,[21] in 1925, stated that there is no proof of a transmutation of sapophytes into tubercle bacilli or a reversion of tubercle bacilli into paratubercle bacilli. Suyenaga [22] attempted to produce a non-acid-fast stain by rapid transfers over a long period of time for 340 generations, but reports only a slight (although definite) loss of acid fastness.

EXPERIMENTS

Only a few type experiments will be described, because space will not permit of much detail when there were several hundred animals used and many thousand cultures made and studied.

I will pass over the large group of acute growing forms obtained from the old cultures with the statement that there has not been sufficient evidence to rule out contaminating organisms that may have been associated with the acid-fast form in the lesion and subsequently carried over into the cultures. Special cultures were prepared in which all tests and controls were made to rule out contamination, and the probability of contamination was reduced to a minimum. The results of a few of the experiments with these "pure" bacilli will be reported.

Two cultures were obtained from an organism obtained from a patient, one of a group of cultures that were prepared with extreme care to rule out possible contamination. The transplants were made early on new tubes, and at no time were we able to obtain rapid growths on various mediums used, at the time the cultures were made. Transplants were

18. Sweany, H. C., and Pinner, Max: J. Infect. Dis. **37**: 340 (Oct.) 1925.
19. Stockwell, W. M.: Am. Rev. Tuberc. **12**: 371 (Dec.) 1925.
20. Ramond, F., and Ravant, P.: Progrès. méd., Dec. 1, 1900.
21. Calmette, A.: Am. Rev. Tuberc. **12**: 355 (Dec.) 1925.
22. Suyenaga, B.: Am. Rev. Tuberc. **12**: 260 (Nov.) 1925.

then made, on various unfavorable mediums, in a specially devised cabinet to preclude contamination. As we had observed previously that there were more bizarre shapes on certain sugar mediums, we planted a small plaque on eight of the more common sugars in Smith tubes plugged with cotton, soaked in hot paraffin, and capped and incubated, Dec. 5, 1925. No change occurred until about three weeks had passed. The inulin and mannite tubes began to show turbidity and a sediment, while all the tubes began to show a thin pellicle of tubercle bacilli. These tubes were carefully opened and the cultures plated out and stains made. The turbidity in the inulin and mannite was caused by a non-acid-fast, gram-positive, motile bacillus that was identical to the parent tubercle bacillus morphologically, but it was not acid-fast. The resemblance in size, length, curving and granulation was striking. This organism did not ferment sugars, and very slowly acidified milk. It had a tendency to form granules, and on a solid medium the appearance was whitish and moderately luxuriant microscopically, and in older cultures microscopically it resembled the staphylococcus. The bacillary forms soon disappeared on solid mediums. In about five weeks, the growth in dextrose began to be turbid; it was examined and found to be a sarciniform growth of a large organism, 1 micron in diameter. By plating this out on a special rabbit serum agar, we obtained two types of organisms, one a tetrad or sarciniform growth and the other a barred organism that resembled a diphtheroid. The colonies of the latter were microscopic, measuring about 30 to 40 microns in diameter.

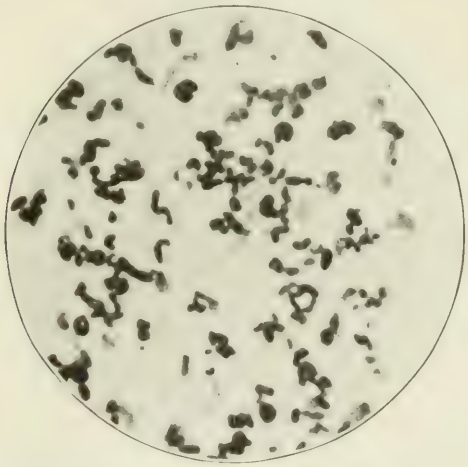


Fig. 1.—A rapidly growing organism obtained from the R 1 culture of the Saranac laboratory, originally isolated by Trudeau thirty years ago, × 1,200.

Many times we have found growth with the low power microscope that we were not able to see with the eye. We were not able to grow this organism beyond the second generation. In general, it was observed that the nearer the tubercle

bacillus these organisms appeared to be, the more difficult they were to grow and the more likely they were to be gram positive and virulent. The animals inoculated with the first bacillary strain are still living, after sixty-five days. The large coccus killed a guinea-pig, in from five to six days, of an acute inflammatory condition usually beginning in the liver and the gallbladder and extending down into the intestines, causing a duodenitis, enteritis and glandular hypertrophy of the mesenteric glands and a terminal pneumonia. This is a characteristic course for these infections to pursue. If the forms are more chronic, the spleen and hilum glands become involved.

In the experiments conducted on pleural exudates, there is a remarkable resemblance in results to those obtained by Karwacki. We found also that no two fluids were exactly alike, and that the acute growing organisms obtained varied within wide limits. Some resembled the common forms found on stock cultures; others were coccus-like, nearly all of which became pigmented in old age, varying from a lemon yellow to an orange, old rose and red. Some were diphtheroid in morphology and were gram positive. I will describe one of these:

Culture 3 was obtained from the pleural fluid of patient C, Sept. 3, 1925, and planted on various mediums. Only acid-fast bacilli and granules were found on direct examination. A partial list of cultural reactions of a bacillus obtained on the blood mediums follows: There was scant growth on all mediums except blood and serum. There was a slight green hemolysis of blood, with very small clear colonies on the agars. There was a slight turbidity in the bouillons. The culture did not grow on gelatin, form indol, reduce nitrates, or form ammonia. It alkalized milk very slowly, with no clotting or protalysis. It formed acid in levulose, dextrose, mannite, galactose, sucrose and salicin, but no gas was formed in any of the sugars. The organism was gram positive and had a diphtheroid form in the dextrose serum-glycerin bouillon. It killed guinea-pigs, producing a "sugar coated" spleen and very small atypical tubercles over the intestines and liver. The lungs were pneumonic (figs. 2, 3 and 4).

Equally interesting are the results obtained on other tuberculous exudates, including spinal fluids and cold abscesses. For some of these I am indebted to Dr. E. J. Berkheiser. The organisms obtained were quite variable, as with pleural exudates. The most interesting observation was that, just as Vaudremer,[23] and Valtis [24] have described filter passing forms of organisms that produce a tuberculosis-like pathologic change, so there

23. Vaudremer, A.: Medicine **3**: 622, 1922.
24. Valtis, J.: Ann. d. l'Inst. Pasteur **38**: 453, 1924.

is good evidence also that there are filter passing mutants that produce a disease in guinea-pigs resembling that produced by the coccus-like mutant previously described. Some fluid filtrates kill the animal in a few days of an acute disease similar to that produced by the coccoid mutants. In fact, the question is raised whether the organisms or granules that pass through the filter are not capable of reverting to the acid-fast form, as Much has suggested for the larger granules. If these animals survive the acute attack, an atypical tuberculosis develops in the lesions of which may be found acid-fast forms, non-acid-fast forms and granules. We have proved (in unpublished work) that the non-acid-fast forms of Much can assume a stage of

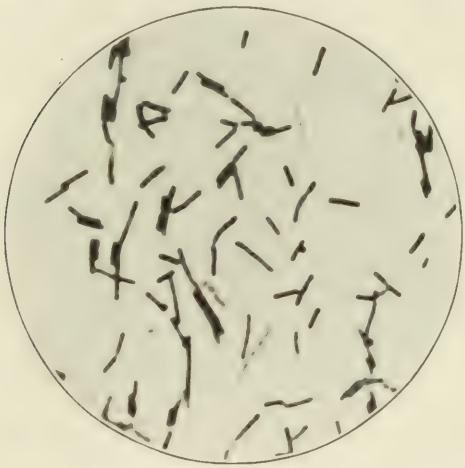


Fig. 2.—Glucose bouillon culture of pleural fluid from patient C, × 1,200.

development between the acid-fast and non-acid-fast forms, passing either into the acid-fast forms or into coccoid or bacillary mutants, depending on the environment.

Just how far these organisms can develop as cocci and still revert back to tubercle bacilli we have not sufficient evidence to prove. There are some suggestive instances in which it seems that non-acid-fast cocci can actually form into acid-fast forms. For example, it has been observed repeatedly that groups of cocci found in animal organs will contain one, two or more partially acid-fast organisms in which it seems they have taken on the acid fastness in growing. These groups have been seen to contain increasing numbers of such acid-fast forms until, apparently, the whole mass has

become a group of acid-fast cocci that in time appear to lengthen out into bacilli. Some of these forms are very small, perhaps filter passing. Such observations are made more frequently on guinea-pigs inoculated with tuberculous pus than those inoculated with pure cultures of tubercle bacilli. This phenomenon is deserving of more study.

It must be pointed out here that the principles underlying these changes are not understood, and no definite rules can be formulated in bringing about these various changes. Two things are necessary, however, before any results can be obtained: first, the organisms must vegetate, that is, the organism must grow, for an experiment may be called negative only when it was a "no growth"; and, second, the environment must be unfavorable. It is well to use a large number of mediums [25] and many cultures to obtain results. For the sprouting of Much's granules, we find that physiologic sodium chloride solution is good to initiate the process. By placing in salt solution and studying simultaneously under the dark field and by staining, we can follow out the changes readily. Transplants must be made in mediums to obtain permanent cultures. We have observed these granules to sprout into motile bacillary forms and also to divide into cocci, thus accounting for the two general types of morphology of the mutants. Furthermore, these forms are sometimes interchangeable, depending on some shift of mechanism that we have not yet solved. In an old abscess, it is difficult to obtain motile sprouts; the tendency in these partially degenerate forms is to develop into nonmotile coccoid forms of low pathogenicity.

In order to substantiate these observations, we undertook a series of experiments in which we buried celloidin capsules [26] containing tubercle bacilli in the peritoneal cavities of guinea-pigs. Many of these capsules became digested until they contained cellular material, but a few persisted intact so that observations could be made. In some of the capsules containing "certified bacilli" or bacilli that we felt were surely pure, diplococci, streptococci and tetrads were observed directly. Others were placed in salt solution, and the division was watched under the dark field and stained simultaneously. The very refractile granules after about twelve hours would appear distinctly double (most of the granules of tubercle bacilli have from one to four nuclei that

25. Space does not permit a description of all these mediums.

26. Silk lawn sacs were made and dipped in 8 per cent celloidin, hardened in 50 per cent alcohol, inoculated, sealed and buried in the peritoneum of guinea-pigs through lateral incisions in the abdominal wall.

do not show unless by careful focusing). Then tetrads would appear. If cultures of these forms are taken at this time on various mediums, some will reproduce pure cultures of tetrads and grow readily after several transfers, while others die out in spite of all efforts. In this respect they resemble the growing of tubercle bacilli themselves that Corper,[27] Griffith [28] and others have shown to be quite capricious in growth, especially during their early abode on artificial mediums.

The cultural characteristics of these cocci were quite variable. Apparently, as they approached saprophytism they gained in ability to ferment sugars, and they grew more rapidly and luxuriantly on artificial mediums. By continued culturing on an artificial medium, many

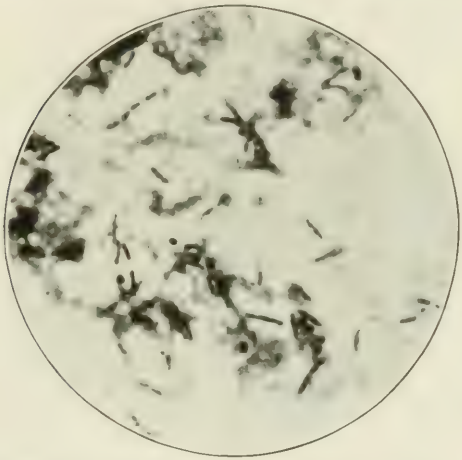


Fig. 3.—Litmus milk culture from pleural fluid from patient C, × 1,200.

gain fermenting power while others die out. As a general rule, the organism that first comes off from the bacillus does not ferment sugars at all and if it does, only acid is formed in dextrose and perhaps levulose. They were most frequently gram positive, although some were gram negative. Some were slightly pathogenic but by continued passage were not able to regenerate acid-fast forms with any degree of regularity. A few experiments indicate that some of these cocci appear to produce a tuberculosis with a return of acid fastness. It may be possible to regenerate tubercle bacilli from cocci that have been removed only a few generations from the granules of Much, provided the conditions of growth are suitable. If such does happen, however, it is not the rule.

27. Corper, H. J.: Am. Rev. Tuberc. **3**: 461 (Oct.) 1919.
28. Griffith, A. S.: Tubercle **5**: 569 (Sept.) 1924.

The following protocol of one culture is an illustration:

A certified culture was placed in a special celloidin capsule and embedded in the peritoneal cavity of a guinea-pig, together with an empty control capsule. In eight days the guinea-pig was killed, and the capsules were removed aseptically, and cultures for acute growing organisms were taken. The control was always negative, while on the eighth day in the cultures from the other capsule a sticky sediment began to show in the dextrose glycerin-serum bouillon tubes, and a few colonies also appeared on the glycerin serum agar. All other cultures were negative. Transplants grew well only on mediums containing serum. Milk was not changed in ten days. A very slight sediment appeared in the plain bouillons. The sugar bouillons became slightly murky, and the only

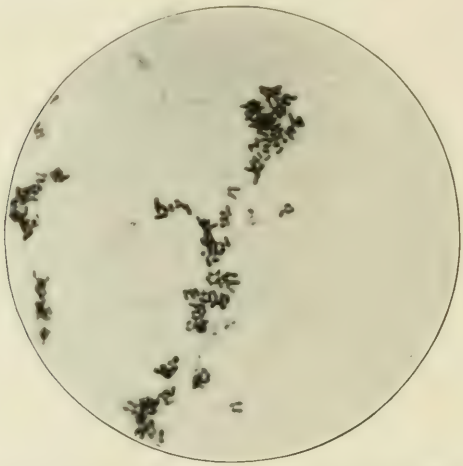


Fig. 4.—Liver serum bouillon culture from pleural fluid from patient C, × 1,200.

sugar that was fermented was levulose. The fermentation began in the butt, and only after three days was it complete in the arm. The organism grew as a two columned streptococcus or as chains of tetrads. It was gram positive and nonmotile.

COMMENT

There is no mystery about the fact that tubercle bacilli are capable of developing into forms of life different from the classic type. It would be contrary to all biologic experience if this did not happen. The work of Mellon,[29] Crowell[30] and Jordan[31] on other bacteria abundantly corroborates this view.

29. Mellon, R. R.: J. Bacteriol. **10**: 481 (Sept.) 1925; **10**: 579 (Nov.) 1925; **11**: 203 (March) 1926.
30. Crowell, M. J.: J. Bacteriol. **11**: 65 (Jan.) 1926.
31. Jordan, E. O.: Interconvertibility of Rough and Smooth Bacterial Types, J. A. M. A. **86**: 177 (Jan. 16) 1926.

Our chief concern in this report is the extent that these forms enter into human disease. Leaving out of consideration the forms that have been described by Ferran, Auclair, Stockwell and others as of unimproved origin, I have shown that a specially purified culture of fresh organisms can be made to produce bacillary forms (diphtheroids and solids) and coccoid forms (diplococci and tetrads) that are not acid fast and do not produce a disease typical of tuberculosis after a single passage. These forms resemble in many respects the forms found in tuberculous sinuses. In fact, it is very probable that many tetrad forms found in tuberculous lesions are mutants of the tubercle bacillus. It is significant that most descriptions of the tetrad organism have been in tuberculous cavities or sinuses (Koch-Gaffky). This question presents an epidemiologic problem worthy of investigation, especially regarding tuberculous infection.

This work also lends support to the Fraenkel-Much theory regarding the origin of Hodgkin's disease from tuberculosis. A great variety of diphtheroid mutants have been found to originate from tubercle bacilli, so it is possible that a certain grade of virulence develops that in some hosts may produce the entity known as lymphogranulomatosis. It is possible also that other diseases, such as polyserositis and Pick's cirrhosis, may be caused by such organisms. These ideas are worth bearing in mind in future research. Artificial mediums and the long continued variations in temperature, oxygen and moisture develop forms that are easily changed, although the more stable fresh cultures can also be altered. In the human body, the part played by the host is perhaps more important than the inherent bacillary properties of variation. Karwacki's suggestions that the lipases and antibodies are responsible for these variations may be accepted as a partial explanation at least. It is a common observation that tubercle bacilli suspended in certain pleural exudates very soon become non-acid-fast granular and coccoid morphology.

There seems to be good reason to believe that the classic acid-fast form of bacillus is not the only cause of pathologic change in tuberculosis and its complications, and even when it is the sole cause, that the type of organism and the type of reaction of the immunizing forces of the host on the organism influence the pathologic condition and clinical course within wide limits.

Regarding the forms described by Ferran and others, I am not prepared to offer a final statement. There is very good evidence that these forms originate from Koch forms because they are associated in tuberculous

lesions (sterile pleural fluids, caseous tubercles, etc.) in which it seems improbable that a concomitant symbiotic infection could occur. Further than this, the fact that they have been produced in all old cultures regardless of origin is making the evidence considerable if not overwhelming.

SUMMARY

1. In a study of various conditions under which mutation forms of the tubercle bacillus may develop, it is found that mutation takes place with regularity during vegetation, depending on the fundamental law of variation together with a particular alteration of environment.

2. A constant favorable environment is difficult to maintain for a long period of time either in old cultures or lesions. In either instance, split forms may appear that are vastly different from the tubercle bacillus.

3. Accordingly, there are produced mutation forms that may assume a great variety of cultural, morphologic and pathologic characteristics.

4. The two most common types of mutants are the bacillary and the coccoid forms, although filter passing forms also appear to exist.

5. Bacillary forms may pass over into coccoid forms and granules, and coccoid forms may grow into bacilli if the medium is suitable.

6. The mutation forms appear to develop from some of the gram-positive granules, which are perhaps resting stages of tubercle bacilli. When cocci are formed, there is a tendency to develop first diplococci, and later various tetrads and staphylococcus-like forms may develop. Bacillary forms also may develop.

7. Many of these mutants are not pathogenic. Many are of low pathogenicity, while others undoubtedly play a definite rôle in disease processes.

8. The suggestion is offered that certain chronic diseases (like Hodgkin's disease and polyserositis) may be caused by mutation forms of tubercle bacilli.

In conclusion the author wishes to thank his assistants, Messrs. Michael Wasick and Maxevanoff, for technical assistance rendered.

North Crawford and Bryn Mawr Avenues.

March 8, 1926.

THE SOURCE OF GLYCOGEN IN TUBERCLES*

MAX PINNER

Since Ehrlich's first communication on the iodophile substance in leukocytes, much work has been done on the distribution of glycogen in normal and pathologic tissues. The first reference to tuberculosis is found in a paper by Langhans,[1] who briefly mentions that he never found glycogen in tubercles. In elaboration of Ehrlich's statements, Katsurada,[2] Best[3] and several other investigators report the increase of glycogen in all inflammatory foci. Gierke[4] found glycogen in the outer borders of tubercles with central necrosis in both polymorphonuclear and mononuclear cells, independent of the localization of the tubercle. The occurrence was more marked in acute than in chronic processes. He conceives the glycogenic infiltration as a manifestation of increased metabolic activity. Lubarsch[5] found in most tuberculous products no glycogen, only occasionally in epithelioid cells and leukocytes and once in a giant cell; most frequently in young tubercles from ten to twenty days after infection in guinea-pigs. Still younger tubercles from four to six days after infection were always free from glycogen. Devaux[6] studied the question again in experimental tuberculosis. According to this author, the necrotic foci are always free from glycogen, but the cellular borders of necrotic foci contain a considerable amount of glycogen in leukocytes and epithelioid cells. No glycogen was found in lymphocytes. Tubercles without a central necrosis never contained glycogen. In cells which had engulfed tubercle bacilli more glycogen was found on an average. W. and M. Pagel[7] found the exudate cells in caseous pneumonia always free from glycogen; they found, as did the earlier investigators, glycogen in the cellular borders of tubercles, especially of the exudative type. Much of the glycogen was extracellu-

* From the Research Laboratories of the Municipal Tuberculosis Sanitarium, and from the Department of Pathology and Bacteriology, University of Illinois College of Medicine.

1. Langhans: Virchows Arch. f. path Anat. **120**:28, 1890.

2. Katsurada: Beitr. z. path. Anat. u. z. allg. Pathol. **32**:193, 1902.

3. Best, F.: Beitr. z. path. Anat. u. z. allg. Pathol. **33**:585, 1903.

4. Gierke, von E.: Beitr. z. path. Anat. u. z. allg. Pathol. **37**:502, 1905; Ergebn. d. Pathol. **11**:871, 1907.

5. Lubarsch, O.: Virchows Arch. f. path, Anat. **183**:188, 1906

6. Devaux, C.: Beitr. z. path. Anat. u. z. allg. Pathol. **41**:596, 1907.

7. Pagel, W., and M.: Virchows Arch. f. path. Anat. **256**:629, 1925.

lar but always in definite relation to cellular detritus. The intracellular glycogen was seen in mononuclear round cells and in leukocytes. Arndt [8] made his studies on domesticated animals, and reported essentially the same results as the previous workers.

Summarizing the experience of the various workers, one finds agreement on the point that not too young tubercles contain glycogen in some epithelioid cells, sometimes in giant cells and rather regularly in leukocytes. That emigrated leukocytes which wander to an inflammatory focus always contain a considerable amount of glycogen, is a well established fact. It is, however, unexplained as yet why epithelioid and giant cells sometimes contain glycogen and why the same cell types more frequently do not contain this substance; and secondly, what the source of the deposit of glycogen in these cells is. In an attempt to solve these questions the following work was undertaken.

METHODS

A series of rabbits was infected intravenously with bovine bacilli of low virulence and killed six, seven, eight, nine, ten, twelve, fourteen, seventeen and twenty days after the infection. Some tuberculous organs of guinea-pigs were examined thirty days after infection, and some human material from necropsies. A series of guinea-pigs received 0.5 cc. of old tuberculin subcutaneously thirty days after infection; they were killed from five to six hours after the injection of tuberculin, when they exhibited all the signs of a severe tuberculin shock.

Small pieces of tissue, not thicker than 3 mm., were fixed either in absolute alcohol or, according to Neukirch,[9] in a saturated solution of glucose in 40 per cent formaldehyde. Since the latter method of fixation prevents better the diffusion to one side of the cell, it was used exclusively in the course of these studies. After embedding in celloidin, sections from 5 to 6 microns thick were cut and stained by Best's [10] carmine stain.

RESULTS

In very young tubercles, about up to the eighth or tenth day after injection, no glycogen was found. In older tubercles, glycogen is seen regularly in the leukocytes of the outer zone. At the same time, and increasingly so with the age of the tubercle, glycogen appears in epithelioid cells as small droplets and occasionally in giant cells. In these serial examinations it was easy to follow the appearance of glycogen in the last two cell types: whenever there is phagocytosis of a glycogen

8. Arndt: Klin. Wchnschr. **41**:39, 1925.
9. Neukirch, P.: Virchows Arch. f. path. Anat. **200**:73, 1910.
10. Best, F.: Ztschr. f. wissensch. Mikrosk. **23**:319, 1906.

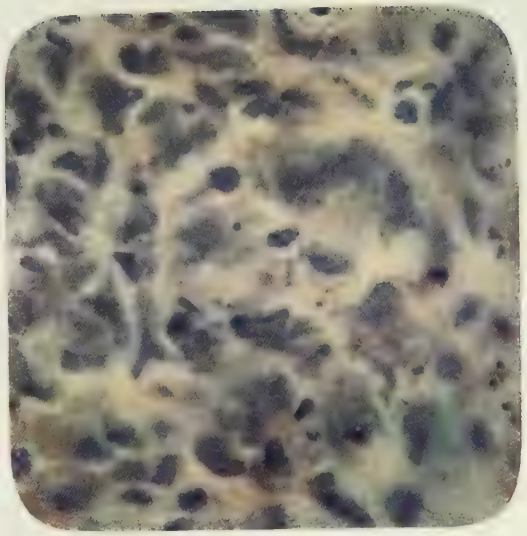


Figure 1

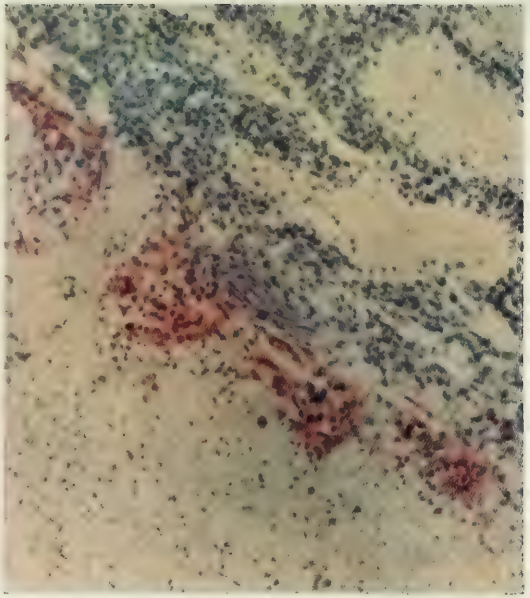


Figure 2

Fig. 1. Liver tubercle in a rabbit, seventeen days after infection by the intravenous route, showing a young giant cell containing pyknotic nuclear fragments of a polymorphonuclear leukocyte and a drop of glycogen. Celloidin sections stained by Best's alkaline carmine.

Fig. 2.—Splenic tubercle in a guinea-pig killed during a severe tuberculin reaction thirty days after infection. Around the caseous center is a red zone of glycogen containing polymorphonuclear leukocytes which immigrate into the focus during the tuberculin shock. Celloidin sections stained by Best's alkaline carmine.

containing leukocyte, its glycogen appears as a small droplet in the phagocyte. The complete development can be followed; a complete and unaltered leukocyte is engulfed in an epithelioid cell; only the pyknotic fragments of a leukocytic nucleus and a drop of glycogen are seen in the phagocyte (fig. 1); the nuclear fragments disappear and only the glycogen remains as evidence of the phagocytic activity of the cell. How strictly the presence of glycogen is dependent on the emigrated leukocytes is well demonstrated in tubercles from guinea-pigs which were killed in tuberculin shock. The marked leukocytic infiltration of the cellular zones in this stage is shown in the carmine stained section by a bright red ring of glycogen containing leukocytes (fig. 2). The necrotic center of tubercles is usually free from glycogen; sometimes small amorphous granules are seen.

The fact that epithelioid cells frequently envelop leukocytes and digest them until to all appearances nothing is left but their glycogen, shows significantly the vital activity of these cells in tubercles, and is a strong argument against that conception which represents epithelioid cells as devitalized or degenerated forms of reticulo-endothelial or monocytic cells.

Livers studded with tubercles seem to contain less glycogen in their parenchymatous cells than a normal organ, but a definite statement cannot be made to this point without a careful control of the alimentary condition. It was rather regularly observed that the liver cells bordering on necrotic tubercles contained much more glycogen than similar cells further removed from the foci. No explanation for this occurrence is suggested.

CONCLUSIONS

Glycogen appears in tubercles when leukocytes immigrate; it is found in epithelioid cells and in giant cells whenever they engulf leukocytes; and the occasional droplets of glycogen in these cells seem to be the remains of the digested leukocytes. Warkany [11] found that dried tubercle bacilli contain 4.1 per cent of glycogen. The possibility must be considered that small amounts of glycogen may be derived from digested bacilli. Devaux's statement that cells containing tubercle bacilli show a tendency to glycogen deposits may lend some support to this concept. It is obvious that only a minimal part of the glycogen found in tubercles can be accounted for by this occurrence.

---

11. Warkany, J.: Ztschr. f. Tuberk. **42**:184, 1925.

SUMMARY

Glycogen is found in tubercles either in leukocytes, or in epithelioid or giant cells. The latter derive their glycogen from leukocytes that have undergone phagocytosis.

By their marked phagocytic and digestive action on leukocytes, the epithelioid cells in tubercles manifest that, though transformed cells, they have retained their functional vitality.

I wish to express my thanks to Dr. R. H. Jaffe, under whose direction this work was done.

April 12, 1926.

DISTRIBUTION OF CERTAIN ANTIGENS IN THE BODY

ETHEL B. PERRY

AND

L. HEKTOEN

Precipitin tests of the organ extracts and various fluids of rabbits after intravenous injections of human hemoglobin and beef lens were made with antiserums for these antigens. No essential differences in their distribution appeared. In pure solutions they both disappeared from the blood and from the organs in about twenty-four hours, but after injections of whole citrated blood, hemoglobin was detected as late as seventy-two hours in the serum and occasionally also in the liver and bile.

Within one-half hour the antigens appeared in the bile, urine, intestinal mucosa and contents, and in different degrees in practically all tissues, revealing not only a general distribution, but also the excretion of a certain portion of antigen unchanged.

The highest concentrations in the organs were in the kidney, bone marrow and omentum; the liver and lymph nodes came next, and the spleen was usually negative after the first few hours.

The relations between the liver and bile were less regular than between the kidney and urine, probably because only a single test of bile could be made while all of the urine could be collected. The antigen content of the fluids and extracts, in general, paralleled that of the serum, but in lower concentrations, and all titers decreased steadily without indication of progressive accumulation or of prolonged retention in any organ.

These results differ from those described by others for cellular antigens only in the shifting of the site of greatest content from the spleen and liver, to the kidney, marrow and omentum. The omentum, known to be rich in clasmatocytes, has been omitted from many studies of antigen distribution.

April 12, 1926.

STREPTOCOCCUS ERYSIPELATIS TOXIN AND ANTITOXIN

HARRY A. SINGER
AND
BERTHA KAPLAN

In attempts to produce local blanching of erysipelas lesions by erysipelas convalescent serum, it was observed that although complete disappearance of the inflammation did not occur at the site of inoculation of the serum, a beneficial effect did result. This neutralizing effect is attributed to bodies in the convalescent serum.

In order to study these immune bodies further, a preliminary study was made of skin reactions in patients with erysipelas, using a sterile toxic filtrate of a culture of *Streptococcus erysipelatis*. It was noted in a series of erysipelas cases that as the disease subsided the skin reactions using the same amounts and concentrations of toxic filtrate became less and less marked or entirely negative.

Since the filtrate employed resembled in its properties the Dick scarlet fever toxin in regard to the skin reactions provoked and in its resistance to heat, it seemed that it might contain a true toxin. If this were the case, the filtrate (toxin) should, when injected into animals or man, be capable of producing within the body a neutralizing substance (antitoxin).

Two highly susceptible persons were immunized by injections of increasing doses of erysipelas sterile filtrate (toxin), the immunity being indicated by decreasing sensitiveness to increasing skin doses. Serum collected before the inoculations were begun failed to neutralize erysipelas or scarlet fever toxin in dilutions of 1:100, whereas following the immunization, the serum from the same persons exerted a powerful neutralizing effect on not only diluted but also undiluted toxin of both the erysipelas and scarlet fever types.

Further neutralization studies showed a greater protective value of the artificially produced immune erysipelas serum (antitoxin) as compared with that of the convalescent erysipelas serum. Blanching, using now the antitoxin in place of the convalescent serum, occurred in 50 per cent of the cases tested, indicating again a relatively higher potency of the antitoxin. From a study of the literature, especially of the work of Rivers and of Birkhaug, the impression was gained that the serum obtained by inoculation of toxin alone compared favorably in its protective qualities with the anti-erysipelas serum produced by inoculation of the organisms.

Cross neutralization tests using various combinations of erysipelas and scarlet fever toxin and antitoxin led to the conclusion that absolute specificity was lacking. However, it should be borne in mind that throughout the work, in order to obtain comparative results in neutralization experiments, but two strains of *Streptococcus erysipelatis* were used and but one strain of scarlet fever streptococcus. It is conceivable that the strains employed belong to the small group of nonspecific hemolytic streptococci described by other workers in their classifications on the basis of various biologic tests.

CONCLUSIONS

The sterile toxic filtrate of a broth culture of *Streptococcus erysipelatis* possesses the properties of a true toxin.

The erysipelas toxin is capable when injected into man of provoking the formation of a neutralizing substance (antitoxin).

The artificially produced immune serum (antitoxin) has a greater potency than convalescent erysipelas serum.

The antitoxin produced by injections of toxin alone seems to compare in its protective qualities with anti-erysipelas serum obtained by others from animals by the injection of organisms.

The hemolytic streptococci of erysipelas and scarlet fever are not biologically absolutely specific.

April 12, 1926.

SYPHILIS OF THE LUNG

WITH A REPORT OF A CASE *

GEORGE J. RUKSTINAT

"Phthisis a lue venera," was a fairly common diagnosis in the sixteenth, seventeenth and eighteenth centuries, and Paré, Borehare, Laennec, Morgagni, DePaul and Virchow are some of the men who recognized the condition. Following the clear differentiation of syphilis from gonorrhea and soft chancre by Ricord,[1] and the discovery of the tubercle bacillus by Koch in 1882, skepticism marked the attitude of most clinicians and pathologists toward pulmonary lesions previously considered syphilitic. The widespread application of the Wassermann test, and the discovery of *Spirochaeta pallida* have greatly increased the reliability of diagnoses in the twentieth century. Warthin's [2] high figures for incidence of syphilitic infection suggest the possibility of frequent pulmonary involvement.

A review of the literature on pulmonary syphilis reveals about five generally accepted types of the disease in the acquired form: the gumma, according to Warthin, the rarest lesion, but still the one on which the frequency of syphilitic infection in an organ is based; chronic interstitial pneumonia, gradually leading to another type, extensive pulmonary sclerosis; bronchopneumonia, and a mixed form sometimes called "syphi-

---

* From the Pathological Laboratory of Rush Medical College.

1. Ricord, P.: A Practical Treatise on Venereal Diseases, trans. by S. Doane, 1852, ed. 6, V. S. Redfield, Clinton Hall, N. Y.

2. Warthin, A. S.: The New Pathology of Syphilis Am. J. Syph. **2**:425, 1918.

litic phthisis," in which pneumonia, gummas, fibrous changes, cavity formation and bronchiectasis may coexist with gangrene at times added where there is secondary infection.

Elizalde,[3] in an extensive study of pulmonary syphilis in thirty adults, describes four stages which he thinks are well defined and analogous to the stages of lobar pneumonia but slower in evolution. The first stage is characterized by an acute productive process, vascular dilatation, exudation, predominantly serous, with a little fibrin perhaps, and a few leukocytes, so there is a beginning consolidation. A little later there is a destruction of the leukocytes by clasmatocytes, and then a multiplication of fibroblasts in the interalveolar spaces and about the blood vessels and bronchi. Small lymphocytes are little in evidence and plasma cells are rare. The exudation after a time reduces the caliber of the vessels, and then the second stage is at hand. A rapid change occurs in cellular types. Lymphoid cells of various sizes and plasma cells form special aggregations in the vicinity of the blood vessels and bronchi and have the microscopic characteristics of miliary gummas. The striking feature is that there is no new formation of blood vessels to nourish the cells which then decay. In the succeeding period there is a fragmentation of the elastic fibers of the blood vessels and bronchi and later a destruction so that the bronchi become dilated. Cellular regression and the reestablishment of alveolar permeability are the outstanding features of this stage. In the final stage the fibroblasts are small and have many fibrils. The plasma cells are also small. There are many kinds of lymphoid cells and many are in collections especially about the blood vessels and bronchi. Resolution begins peripherally. There is a desquamation of alveolar epithelium, and pieces of this may be expectorated. Foci of peribronchitis are common, and the lung is contracted.

In twenty-four of this author's cases the syphilitic process was unilateral, both lungs being attacked with similar frequency. Aortic aneurysm was present in 75 per cent of the bodies, causing bronchial compression, and the syphilitic lesion always occurred on the side compressed. Elizalde explains this localization on a basis of decreased pulmonary activity and resistance. In one instance trauma to the lung parenchyma by streptococci with a subsequent anaerobic growth of spirochetes seemed the most plausible explanation. Gummas were invariably found in relation to a blood vessel, and even when numerous spirochetes were found in the interstitial tissue only a pneumonia resulted in the absence of a vessel.

3. Elizalde, P. J.: Anatomia Patologica y Patogenia de la Sifilis Pulmonar. An. de Fac. de med., Montevideo **5**:315. 1920.

Gross descriptions of the lungs in pulmonary syphilis are available, and the following is that of Germain Sée [4]:

The lungs are as it were ploughed with deep furrows, filled with sclerous tissue. These furrows resembling syphilitic cicatrices of the liver, deform the surface of the lung determining more or less marked retraction of the parenchyma. . . . Nodosities are perceptible . . . appearing at the surface or disseminated in the depths of the parenchyma. . . . The alterations are the less pronounced the more the nodosities are wanting and all may be limited to a circumscribed thickening of the pleura and to fibrous bands partitioning off a portion of the lung.

Fowler [5] cites the following gross differences between syphilis and tuberculosis of the lung:

Tubercle usually affects the apex of the lung and subsequently the apex of the lower lobe and tends to progress in a certain route. The primary lesion of syphilis is often about the root and central part of the lung. The disease follows no definite line of march and gummata may be found in any position. Both tuberculosis and gumma may undergo either necrosis and caseation or fibrous transformation, but with caseous tubercle the tendency toward softening and cavity formation is the rule, whereas a caseous gumma very rarely breaks down. The progressive destruction of the lung, by a process of disintegration leading to a gradual increase in the size of a cavity, a change so commonly observed in tuberculous disease, is rarely observed in syphilis except as a secondary result of stenosis of one of the main bronchi. In nearly all cases of advanced destruction of the lung, occurring in the subjects of syphilis, stenosis either of the trachea or of one of the main bronchi is present, whereas this lesion is very rare in tuberculosis. The cavities found in cases of pulmonary syphilis are usually bronchiectatic, but not invariably so; whereas in tuberculosis they are commonly due to progressive destruction of the lung but may be bronchiectatic. The tendency to the formation of pulmonary aneurysm, so marked a feature in tuberculosis is rarely observed in pulmonary syphilis.

Carrera [6] describes the scar of tuberculosis as:

. . . round, sharply delimited with concentric fibers, hyaline and scant in nuclei, devoid of vessels and elastic tissue, less given to anthracotic pigmentation but more frequently calcified and very often confluent. The syphilitic scar is irregular, radiating, more like ordinary connective tissue, still contains blood vessels often with angiectatic capillaries, continuous with the thickened walls of the nearest alveoli, still showing elastic fibers and the outlines of old vessels and alveolar walls and extremely rarely conglomerate. The most conclusive differential point is the finding of collections of plasma cells in the fibrosis of syphilis.

---

4. Sée, G.: Diseases of the Lungs, New York, William Wood and Company, 1885, pp. 260-267.

5. Fowler, in Osler and McCrae: Modern Medicine, ed. 2, Philadelphia, Lee and Febiger, 1914, pp. 171-174.

6. Carrera, J. L.: Syphilis of the Lungs, Pathological Study of the Lungs in 152 Autopsy Cases, Am. J. Syph. **4**:1 (Jan.) 1920.

The histologic differences between tuberculous and syphilitic lesions of the blood vessels have been described in detail by Carrera, and a brief statement of the essential features of each follows. In tuberculosis there is a rather generalized destructive process; the elastic tissue degenerates and does not proliferate in the intima and the muscle fibers of the media degenerate or atrophy. In syphilis the elastic tissue is better preserved and at times is markedly increased in the intima; "round cell" infiltration in the intima is more marked than in tuberculosis and is seen as a distinguishing feature in the media, and in the adventitia there is plasma cell accumulation and new capillary and new "connective tissue" formation.

Warthin,[2] in reporting his "New Pathology of Syphilis," determined syphilis of the lung positively in three cases, but admitted he had not devoted as much time to this organ as he thought necessary. He maintains that the difference in incidence of syphilis recorded is mainly due to a difference in pathologic criteria, and statistics appear to prove this. Claytor,[7] in 1905, found no pulmonary syphilis in 13,000 specimens at the Army Medical Museum in Washington. Symmers,[8] in 4,880 necropsies at Bellevue Hospital, New York, reported syphilis of the lung in 0.24 per cent. Carrera,[6] working in Warthin's laboratory, found microscopic evidence of pulmonary syphilis in 7.8 per cent of 152 bodies having syphilis elsewhere. Osler [9] begins a paragraph on syphilis of the lung with "This is a rare disease," and continues: "In 2,800 postmortems at the Johns Hopkins Hospital there were twelve cases with syphilitic disease in the lungs; in eight of these the lesions were in congenital syphilis." This is an incidence of 0.42 per cent for the total number of cases.

Lord [10] saw only one instance of "indurative pneumonia" associated with syphilitic ulceration of the trachea in 3,000 necropsies at the Massachusetts General Hospital and was doubtful as to the syphilitic character of the lung lesion. Howard,[11] at the University of Iowa hospital, found that 0.55 per cent of 720 bodies on which necropsy was performed had pulmonary syphilis clearly demonstrable histologically, although *Spirochaeta pallida* was not found. This author states that the incidence of

---

7. Claytor, T. A.: Syphilis of the Lung, with a Report of the Anatomical Findings in a Case, Am. J. M. Sc. **129**:563, 1905.

8. Symmers, D.: Late Acquired Syphilis, J. A. M. A. **66**:19 (May 6) 1916.

9. Osler, Sir William, and McCrae, T.: The Principles and Practice of Medicine, ed. 9, 1920, New York, D. Appleton & Company.

10. Lord, F. T.: Diseases of the Bronchi, Lungs and Pleura, Philadelphia, Lea and Febiger, 1915.

11. Howard, C. P.: Pulmonary Syphilis, Am. J. Syph. **8**:1, 1924.

pulmonary syphilis as compared with visceral syphilis elsewhere and exclusive of the nervous system is 1 : 20.

Clinical observers generally record a higher incidence of pulmonary syphilis than pathologists, with the exception of Carrera. Such conclusions are based on an absence of tubercle bacilli in the sputum, positive Wassermann reactions, histories of infection coupled with marked improvement under antisyphilitic treatment and roentgen-ray shadows presumably characteristic in location and configuration. Watkins [12] claims the following roentgenologic differences between syphilis and tuberculosis of the lung:

> Tuberculosis tends to invade the upper lobes. The characteristic shadows are found surrounding the apical or subpleural lobules. The shadows . . . show a definite relation to some branch of the bronchial tree. Syphilis tends to invade the lower and middle lobes and to involve the tissue at the hilum first so that the densest shadow is there, diminishing toward the periphery. The shadows do not bear a distinct relation to the bronchi and at their edges have either a ragged, worm eaten appearance or the lung is evenly speckled; or there are lance-like radiations of dense elastic tissue.

This author rationalizes his interpretations in the light of Carrera's work subsequently.[13]

The Karschners,[14] in 120 cases selected from the literature, in fifty-five of which postmortem examinations were made, found pulmonary syphilis in the ratio of males to females 2 : 1 and the average time of appearance eleven years after the initial lesion. Munro [15] found "The shortest time between infection by the spirochete and symptoms referable to the chest 3.5 years." He bases this statement on a 6 per cent incidence of pulmonary syphilis found in 100 patients examined as a routine at Glenlomond, a tuberculosis hospital. Stanley,[16] basing his conclusions on somewhat more representative figures, says:

> In a series of 1,000 cases, notified as phthisis, I found two certain of syphilis and one doubtful. In the last seven years I have collected fifteen cases, some of which have come to postmortem examination and some are still under observation—observation which confirms the opinion that they are syphilis and not tuberculosis.

---

12. Watkins, W. W.: Roentgen Diagnosis of Lung Syphilis, Am. J. Syph. **1**:760, 1917.

13. Watkins, W. W.: X-Ray Characteristics of Lung Syphilis, J. Radiol. **1**:297, 1920.

14. Karschner, R. G., and Karschner, C. F.: Syphilis of the Lungs, an Analysis of 120 Selected Cases, Ann. Med. **1**:371, 1920.

15. Munro, W. T.: Syphilis of the Lung, Lancet **2**:1376, 1922.

16. Stanley, J. D.: Lung Syphilis, Brit. M. J. **2**:781 (Oct. 7) 1911.

The general attitude toward syphilis of the lungs is apparent from the following statement of Blakeman[17]: "In the presence of syphilitic stigmata, any obscure lung pathology should be considered as syphilitic until proven otherwise." Reports of cases not confirmed by necropsies are naturally of far less significance than those tested out by rigorous histologic methods. The impossibility of applying such methods to patients is apparent, but a greater reticence to accept a case as syphilitic without long, careful observation will lead to a more accurate, reliable compilation of data on an interesting disease process.

REPORT OF CASE

History.—E. L., aged 42, occupation unknown, while riding with a friend in an automobile and apparently in good health, suddenly became ill and died on the way to the Cook County Hospital.

Anatomic Diagnosis (Dr. E. R. LeCount).—Marked syphilitic aortitis; fusiform aneurysm of the root of the aorta; "cor bovinum," giant papillary muscles; huge syphilitic scars of the lungs with compensatory bullous emphysema; syphilitic hepatitis with scarring; scar of the penis; dilated mitral ring; moderate edema of the brain substance, lungs and tracheobronchial lymph glands; marked passive hyperemia of the abdominal viscera; engorged veins of the head; acute slight ascites and moderate bilateral hydrothorax; subpleural and subpericardial petechial hemorrhages; localized subperichondrial hemorrhages of the costal cartilages (agonal?); abrasions of the scalp and left leg; bruise of the right arm; feces-stained perineum; sclerosis of the aortic leaflets; protruding hemorrhoids; marked bilateral fibrous orchitis; chronic catarrhal prostatitis; cysts of the lining of the prostatic part of the urethra; fibrous adhesions between (1) the visceral and parietal layers of the tunica vaginalis sacs, (2) the spleen and diaphragm, (3) the gastrohepatic ligament and gallbladder, (4) the aorta and pulmonary artery; localized bilateral fibrous pleuritis; epitheliosis of the esophagus; hyperplasia of the spleen, inguinal and tracheobronchial lymph glands, lymphoid tissue of the back of the tongue and circumvallate papillae; slightly flaring costal margins; fenestrated pulmonary valve leaflets; vertical furrows of the right lobe of the liver; retrocecal appendix vermiformis, directed upward; moderate hypostatic hyperemia of the lining of the bowel.

Necropsy.—The aorta was thin and dilated at its root and arch so that as it lay in the pericardial sac its wall was folded longitudinally in two places. The circumference of the aorta was 13 cm., 2 cm. distal to the free margins of the aortic leaflets; 7.3 cm. at the distal margin of the innominate artery; 5.4 cm., 2 cm. proximal to the celiac axis and 3.8 cm., 2 cm. distal to the renal arteries. The adventitia of the root of the aorta was pink from a delicate tracery of engorged blood vessels and for its first 6 cm. was stippled with petechial hemorrhages (about 15 per square centimeter). The sinuses of Valsalva were dilated so that there were vertical furrows in the outer surface of the aorta between the pouches opposite the mutual attachments of the aortic valve leaflets. The lining of the sinuses for the coronary arteries was finely wrinkled radially from the mouths of these vessels. The lining of the arch of the aorta was coarsely wrinkled longi-

17. Blakeman, F. W.: Syphilis of the Lung, Canad. M. A. J. **14**:606, 1924.

tudinally and mottled about 20 per cent generally by calcified plaques up to 15 by 10 mm. The linear wrinkles became gradually finer distal to the arch and ended abruptly 10 cm. up from the superior mesenteric artery. The abdominal part of the aorta was coarsely wrinkled for 4 cm. distal to the superior mesenteric artery and between the renal arteries.

The heart with 1.2 cm. of attached aorta and the pulmonary artery to its bifurcation weighed 562 Gm. The subepicardial fat was most abundant in the front of the right ventricle and close to the septum; it was 18 mm. thick at the coronary sulcus. The myocardium was light red-brown and grossly free from fibrous change. There was nothing but fluid blood in the right ventricle. The moderator band was well developed and about 9 mm. in diameter. There were about five fenestrations of each pulmonary valve leaflet near their contiguous edges, the largest 8 by 5 mm. The adventitia and intima of the pulmonary artery were finely wrinkled longitudinally and the lining, in addition, was almost imperceptibly pitted. The left ventricle was firm, with rigor. The mitral ring admitted five fingertips easily. The circumference of the mitral ring was 11.6 cm.; of the tricuspid, 14.5. The maximum thickness of the outer wall of the left ventricle was 31 mm.; of the right, 7. The papillary muscles of the left ventricle were 2.5 by 1.8 cm. at their bases. The free margins of the aortic valve leaflets were from 2 to 3.5 mm. thick, gray-yellow and smooth. The anterior and right posterior aortic leaflets were fused for 12 mm. vertically, and there was a similar fusion of the right and left leaflets for 7 mm. The mitral leaflets were pink-yellow from slight fatty thickening for 8 mm. in diameter at their centers, and their free edges were normally smooth. The coronary arteries had patent mouths, wide lumens and linings thickened by faint linear ridges. There was a wide anastomosis between the circumflex branch of the posterior coronary artery and the anterior coronary artery.

The upper lobe of the right lung was puckered and firm in a rough S-shape of the dorsal part of its thoracic surface; each arm of the S was about 7 cm. long, and it was about 5 cm. high (fig. 1 *A*). This scar was about 1 cm. deep, and coarse indentations of a similar depth or less connected the arms of this *S* and also radiated from them (fig. 1 *B*). The depressions were blue-black, the intervening knobs of tissue pink-gray and firm. The posterior surface of the upper lobe near its root was irregular with alternating purple depressions and pink elevations in which the air sacs were up to 2.5 mm. in diameter. The middle lobe of the right lung was the largest (fig. 1 *C*) and was crepitant throughout. There was a firm mass of adhesions about 2 cm. in diameter between the upper and middle lobes near the peripheral part of the dorsal third of the upper interlobar fissure (fig. 1 *D*). There were also dense patches of fibrous adhesions between the apex of the upper lobe (fig. 1 *E*) and between the ventral edge and mediastinum (fig. 1 *F*). The lower lobe was about one-eighth the size of the median and consisted of about five earlike parts, the largest 6 cm. in diameter and 1 cm. thick (fig. 1 *G*), in which the air spaces were up to 3 mm. in diameter. These lobules were attached to a firm purple-black, shriveled stalk at the root of the lung (fig. 1 *H*). The right lung weighed 847 Gm.; the left, 392. Irregularly-shaped, smooth-topped projections up to 3 cm. in diameter (fig. 2 *A*) sharply defined by constricting bands of fibrous tissue formed the bulk of the upper lobe of the left lung. The peripheral air sacs in these nodules were up to 3 mm. in diameter. Pendant from the center of the costal surface of this lobe was a feathery lavender-red mass 7 by 5.5 by 2 cm. (fig. 2 *B*), in which the air vesi-

cles were up to 7 mm. in diameter. Its stalk was silver gray to black, 40 mm. wide and 2 thick (fig. 2 *C*). The lobes of the left lung were firmly bound together by firm masses of fibrous tissue at the middle of the costal edge of the interlobar fissure (fig. 2 *D*). An emphysematous mass 8 by 6 by 2 cm. formed the lowermost part of the lower lobe (fig. 2 *E*) and was connected by a bridge of

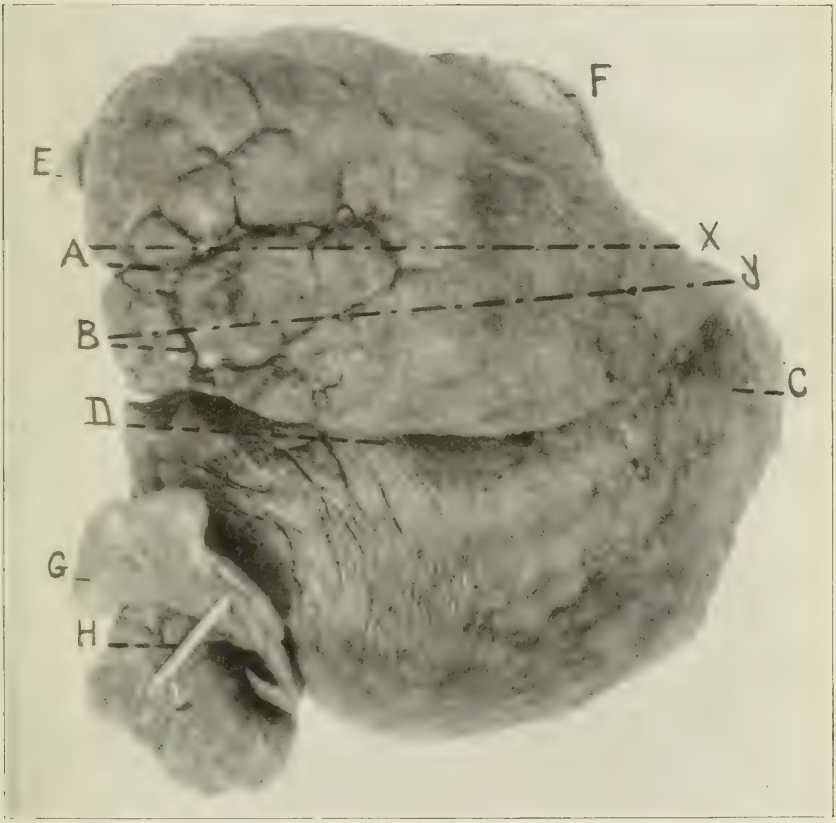


Fig. 1.—The costal surface of the right lung about two-fifths natural size showing: *A* and *B*, the scarring of the upper lobe; *C*, the large middle lobe; *D*, the adhesions between the upper and middle lobes; *E* and *F*, the adhesions at the apex and ventral edge respectively; *G*, the largest bullous component of the lower lobe; *H*, the scar tissue stalk of the bullous components; *X* and *Y*, the location of the photographs in figures 3 and 4, respectively.

fibrous tissue 5 mm. wide and 30 long (fig. 2 *F*) to a similar bullous projection on the ventral edge of the lobe.

The lungs were preserved in formalin after injecting formalin into the pulmonary veins with the arteries tied. On surfaces made by cutting the right lung at its apex there is a firm, slightly elastic yellow-gray nodule 22 by 15 mm. and one 7 by 5 mm. adjacent to it. The nodules are sharply defined, stippled

black, about one-fifteenth in the middle and bordered by firm, pink-gray fibrous tissue continued to puckered indentations of the lung periphery marked by coarse, radiating strands. There is a similar nodule although smaller (fig. 4 *A*) on a surface formed by cutting the upper lobe (fig. 1 *Y*). These pits (fig. 4 *B*) have

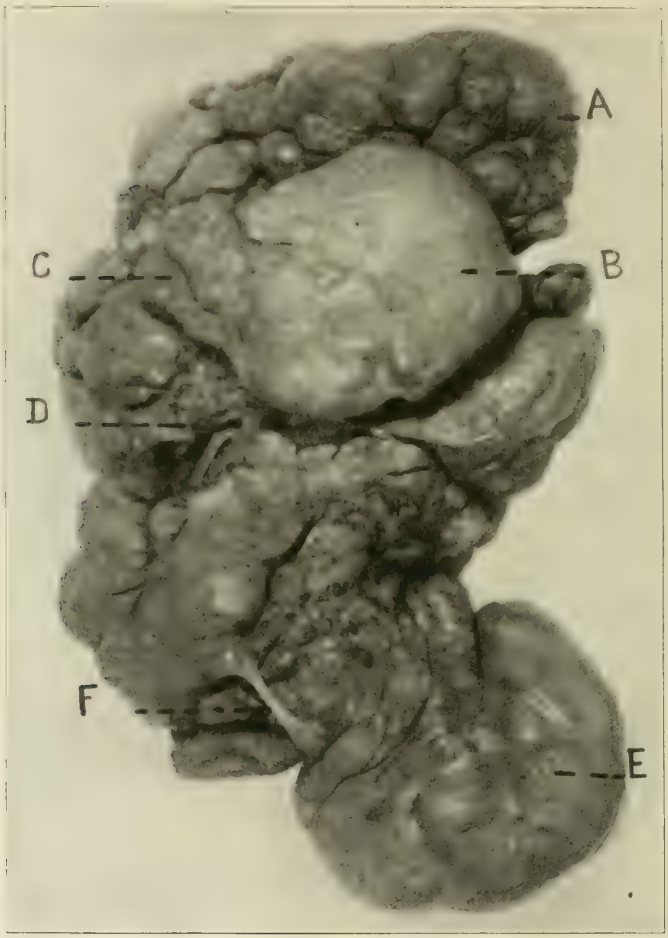


Fig. 2.—The costal surface of the left lung, about one-half natural size, showing: *A*, the irregular projections of emphysematous lung parenchyma; *B*, a huge bullous mass of the upper lobe; *C*, the pedicle of the mass; *D*, the position of the interlobar adhesions; *E*, a bullous mass of the lower lobe; *F*, a firm fibrous tissue strand between two giant emphysematous masses.

markedly puckered walls and are up to 14 mm. deep. Between them are collections of air cells markedly dilated (fig. 4 *C*). Fibrous tissue strands up to 6 mm. wide, irregularly streaked and spotted with coal dust, border the bronchi (fig. 4 *D*) and bridge from these to encircle the blood vessels (fig. 4 *E*) and some of

the nodules described. In several place, as at *F*, figure 4, compressed and elliptical air sacs, their long axes parallel, are included in this fibrous tissue. A nodule 1 cm. in diameter near the hilum contains a branching ingrowth of fibrous tissue continuous with that about a neighboring artery and bronchus (fig.

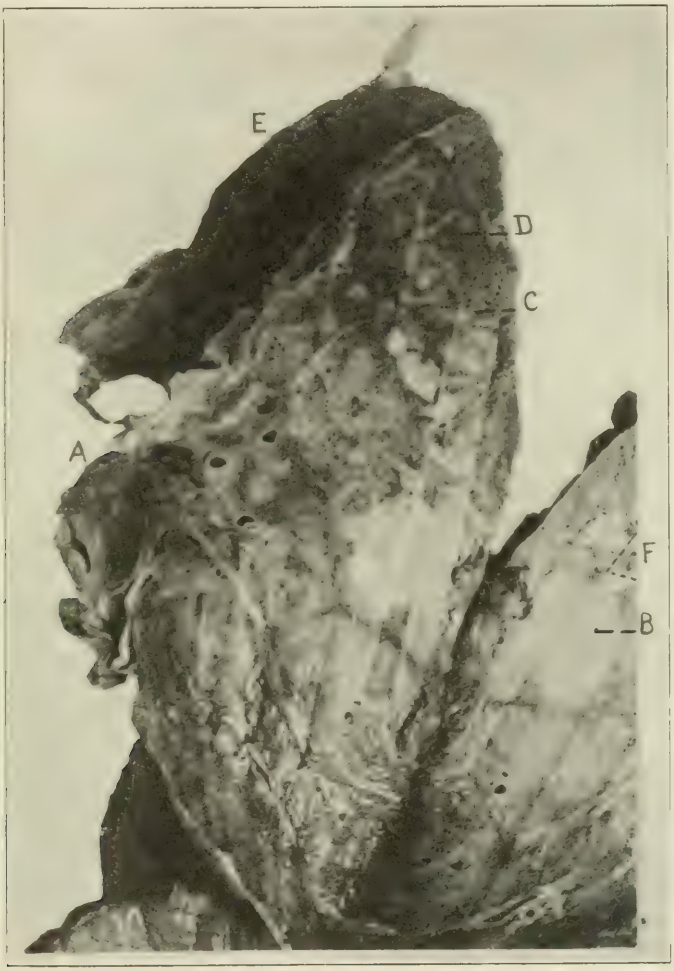


Fig. 3.—A surface formed by cutting the upper lobe of the right lung at "*X*," showing: *A*, the coal-pigmented nodule-containing lymph gland; *B*, the large nodules forming the larger part of this surface; *C*, the islands of dilated alveoli; *D*, the coal-pigmented mass; *E* and *F*, the location of microscopic sections.

4 *G*) and one near it (fig. 4 *H*), 12 by 9 mm., is yellow-brown, friable and fissured at its center. The walls of the blood vessels are markedly thickened, and some arteries with a wall 1 mm. thick have a lumen only 3 in diameter. The lining of the bronchi and bronchioles is markedly wrinkled transversely between lon-

Fig. 4.—A surface formed by cutting the upper lobe of the right lung at *"Y,"* showing: *A*, a typical circumscribed and pigmented nodule; *B*, the puckered pleural pits; *C*, circumscribed emphysematous places; *D*, fibrous tissue masses about the bronchi, and *E*, those about blood vessels; *F*, compressed alveoli in the fibrous tissue; *G*, fibrous tissue ingrowth into a nodule; *H*, a friable and fissured nodule; *I*, markedly wrinkled bronchial mucosa; *J*, location of microscopic section.

gitudinal elevations of mucosa from 1 to 1.5 mm. apart (fig. 4 *I*). The peribronchial lymph glands are about 90 per cent black from coal dust and very firm. One 6 by 12 mm. (fig. 3 *A*) contains two firm gray nodules each 1.5 mm. in diameter and uniformly stippled with coal dust. Surfaces formed by cutting the upper lobe at (*X*) about 1 cm. more cephalad than *Y*, figure 1, are about four-fifths firm nodules (fig. 3 *B*) and interlacing bands of fibrous tissue which hem in islands of air sacs dilated to 5 mm. in diameter and across which threadlike remnants of lung tissue branch (fig. 3 *C*). In one place near the dorsal border

Fig. 5.—A low-power illustration of the edge of a gumma with small lymphocyte and plasma cell infiltration about a bronchiole.

where three or four nodules coalesce there is a firm black place 1.5 cm. in diameter (fig. 3 *D*). The middle lobe of the right lung contains a black nodule 6 mm. in diameter on the middle of the front edge of its interlobar surface. There are only one or two much pigmented nodules in the lower lobe. Because of its marked atrophy, there is an apparent increase in the arteries, which are laced together in many places by scar tissue. The air sacs of its bullous processes are uniformly 1.5 m.. in diameter.

Surfaces formed by cutting the left lung through both lobes vertically and close to the course of the main bronchi are mottled, about equally gray and pink

and speckled with black. The upper lobe is about one-third interlacing bands of fibrous tissue up to 8 mm. wide and about one-third black from coal dust. About the lower and ventral one tenth of the upper lobe is fibrous tissue containing compressed air spaces, as mentioned in the right lung. Collections of these up to 14 by 11 mm. bounded by fibrous tissue form about one third of the surface, and 75 per cent of these sacs are 1 mm. in diameter. The upper two thirds of the front, 1 cm. of the upper lobe, contain air spaces up to 8 mm. in diameter. Nodules, 7 by 5 mm., partially encircled by coal deposits, gray except for slight black stippling and a little orange-yellow pigmentation at the center, are in the scar tissue 8 mm. from the lung apex and at the point of maximum puckering. The lower lobe is crepitant throughout, and its cells are barely visible grossly. Surfaces formed by cutting the earlike projections contain air sacs uniformly 3 mm. in diameter. The fibrous pedicles for these are remarkably twisted.

Paraffin sections stained with hematoxylin and eosin and phosphotungstic acid hematoxylin, in the upper lobe of the right lung show (fig. 4 *H*), in the fissured place a closely packed mass of small lymphocytes surrounded by definite ingrowths of fibrous tissue from the adjoining thickened alveolar walls. These ingrowths contain few blood vessels but an abundance of cells from 5 to 10 per cent of which are plasma cells; the rest are small lymphocytes and fibroblasts. The alveolar walls, two to three times normal thickness, contain many small lymphocytes and a few plasma cells, and the alveoli are about one-third filled by large oval cells with eccentric nuclei and faintly granular cytoplasm. A large bronchus has no noteworthy alteration of its cartilage, but the submucosa near this has many dilated blood vessels and few plasma cells; but the latter and also small lymphocytes are abundant about a bronchial gland and near the basement membrane of the mucosa. In places, edematous young fibrous tissue rich in capillaries has bulged the mucosa inward.

In sections of the upper lobe of the left lung bordering on one of the small firm nodules mentioned, the bronchial walls are frayed in many places, and there is considerable desquamation of the lining epithelium. There is an abundance of small lymphocytes in the interalveolar spaces and in the connective tissue surrounding a homogeneous nodule into which a coal-pigmented sprout projects at one point. Here there are also plasma cells, for the most part scattered diffusely, but in places in clumps of from 10 to 30.

In another section of the upper lobe of the right lung (fig. 3 *E*), the alveoli are markedly dilated and thin-walled, so that the nuclei bulge into the lumens of about one-third of them. In other parts of the section, the alveolar walls are broader, especially near the small arteries whose walls are about twice normal thickness and in the fibrous tissue about which there are many small lymphocytes. Bordering on the last described place is a zone of thick-walled alveoli heavily infiltrated with small lymphocytes, and here the bronchioles are dilated. Into this zone run occasional small strands of fibrous tissue, offshoots from whorls and wider strands containing many small lymphocytes, and a few islands of elongated thick-walled alveoli. A mass, staining pink with eosin, borders this place and is about one-fourth sprinkled with small lymphocytes, and contains a few thick-walled blood vessels, mostly centrally, a few alveolar remnants barely distinguishable and a few fibrous and elastic tissue bands peripherally, but no bronchioles.

In a third section of the right upper lobe (fig. 3 *F*) is an abundance of young fibrous connective tissue containing many small lymphocytes, mostly scattered but in places in clumps around the thick blood vessels. Bordering this place is one in which the fibrous tissue becomes more dense, with fewer nuclei and small lympho-

cytes. This merges with less compact tissue where small lymphocytes are abundant, and from this fibrous sprays pass into a homogeneous mass. In the latter, thick-walled blood vessels and a slight degree of fissuring only are discernible, and small lymphocytes occupy about 5 per cent of the region.

In some places (fig. 4 *J*) the alveolar epithelium is three or four layers thick. Contiguous to such places are collections of small lymphocytes connected with similar masses, surrounding the bronchioles. The internal elastic lamina is the best preserved structure of most of the smaller arteries. The elastic fibers are in places separated by small lymphocytes, and the outermost fibers are frequently broken where there are large collections of lymphocytes in the media. Occasional elastic fibers are in the fibrous tissue generally and pass also into the necrotic places. Fragmented elastic tissue fibers make alveolar outlines perceptible as through a veil in parts of the last mentioned places, in other parts such outlines are reinforced by collections of fibrin. Near many of the gummas fibrin is also abundant in the alveoli.

No tubercle bacilli were found in smears of the bronchial mucus. Stains for spirochetes were not made, as it was thought the optimal time for the demonstration of such organisms had passed before the lungs were thoroughly investigated.

SUMMARY

Acquired pulmonary syphilis with gumma formation is a comparatively rare disease.

The gumma in the lung is in general like the gumma elsewhere, except that in some instances there is a decrease in the width of the peripheral lymphocyte zone.

Spirochaeta pallida has rarely been demonstrated in pulmonary syphilis.

The discrepancy between clinical and necropsy incidence of lung syphilis is due to the more rigid, standardized, histologic criteria used by pathologists.

April 12, 1926.

SKIN REACTIONS WITH THE FILTRATE OF A KOCH STRAIN OF B. TUBERCULOSIS CULTIVATED ON A SYNTHETIC MEDIUM

RUSSELL D. HERROLD
AND
CLARENCE C. SAELHOF

John McCormick Institute for Infectious Diseases, Chicago

The so-called Koch strain of the tubercle bacillus is an avirulent culture which grows profusely on the ordinary mediums. A substance may be formed in a synthetic medium which gives a skin reaction. Results with nutrient broth containing 0.1 per cent of dextrose and 0.1 per cent of dibasic sodium phosphate in place of sodium chloride were reported recently (J. A. M. A.

86:747, 1926). Dr. Novy kindly supplied the culture. It is the strain brought from Dr. Koch's laboratory in 1888, and originally was virulent.

Cultures were made on Long's synthetic medium. After five days the medium was passed through Berkefeld N filters, and the filtrate was diluted with salt solution (0.9 per cent) for the skin tests. One tenth cubic centimeter intracutaneously produced skin reactions in normal persons with dilutions up to 1:50.

Most normal persons in twenty-four hours had redness at the site of injection from 1 to 3 cm. in diameter, the maximum being reached in from twenty-four to forty-eight hours. Often a pigmented spot persisted for several days and sometimes for several weeks. Such reactions were arbitrarily classified as positive, and in degree are one, two, and three plus. Doubtful reactions are from 5 to 10 mm. in diameter, and after forty-eight hours have disappeared. Controls of medium diluted with salt solution were negative.

At present seventeen frank cases of pulmonary tuberculosis, confirmed by stained preparations, have been tested. Of these, sixteen were negative and one slightly positive, as was the control. Subsequent retesting of this person had the same result even with 1:25 and 1:10 dilutions of toxin.

In a series of 33 persons with no clinical tuberculosis, the following results were obtained:

Toxin	Negative	Plus-minus	1 plus	2 plus	3 plus	Control
5 day filtrate 1:50....	1*	1†	11	15	5	neg.

* Underweight, temp. 97 C.
† Temperature 100 in twenty-four hours.

Results with filtrates of five and seven days cultures in eleven consecutive cases were:

7 day 1:100...	+	—	—	±	++	—	—	±	+++	+++	++
5 day 1:50....	++	+	±	+†	++	+†	+†	+†	+++*	+++	++

* Markedly pigmented for two weeks.
† Colored persons.

This test was applied to fourteen students, apparently normal. Of these, four had two and three plus readings, and some roentgen-ray evidence of calcified tuberculosis was found. The ten others had lesions apparently with no calcification, and their reactions were negative. It seems that with healing, less antisubstance is produced by the tubercle to neutralize the injected toxin. However, this series is too small for definite conclusions. The interpretation of these results is tentative. The presence of a reaction in the majority of apparently normal adults seems to indicate that a substance is produced by the growth of this strain of tubercle bacillus in a synthetic medium which acts in a different manner than tuberculin. This is in accord with results reported recently.

Further tests on a large number of patients are indicated with filtrates from a variety of strains of tubercle bacilli. The reaction to the filtrate in normal adults and the absence of a reaction in tuberculous patients may mean that with an active lesion there is sufficient antisubstance to neutralize antigen. According to results with the fourteen patients examined by roentgen ray, apparently there is a relationship between intensity of skin reaction and calcium deposition or healing, because the more severe the reaction, the greater is the calcification and inactivity of the tuberculous lesion.

May 10, 1926.

AN ANOMALOUS BAND ACROSS THE CHANNEL OF THE AORTA AT THE LEVEL OF THE AORTIC LEAFLETS

SEYMOUR WEINSTEIN

From the Pathological Laboratory, Rush Medical College, Chicago

In 1878, Archer (*Dublin J. M. Sc.* **65**:405, 1878) reported a congenital band which stretched loosely across the lumen of the aorta just above the insertion of the leaflets. It arose by an expansion 1.25 cm. wide just above the junction of the posterior and left lateral semilunar leaflets and gradually narrowed becoming inserted at the junction of the posterior and right lateral leaflets. It seemed to consist of the same kind of tissue as the leaflets.

Archer believed that the band developed with the semilunar leaflets, and was to be regarded as an irregular and supernumerary cusp.

In 1896, Röhrle (*Deutsche med. Wchnschr.* **22**:270, 1896) described a more tendinous band in the aorta of a child as the only anomaly of that sort found in 25,000 necropsies at the Foundling's Home in Moscow.

One end was at the left end of the left semilunar cusp, and it stretched tightly across to the left end of the right semilunar cusp. Its ends were thin like threads, and at its center it was 5 mm. in diameter.

In 1900 Hektoen (*Tr. Chicago Path. Soc.* **3**:105, 1900) reported an observation he made of a large defect at the base of one of the aortic cusps, which he ascribed to a defect in the development of the aortic septum. At this time he cited several instances of anomalous cords at the level of the aortic cusps.

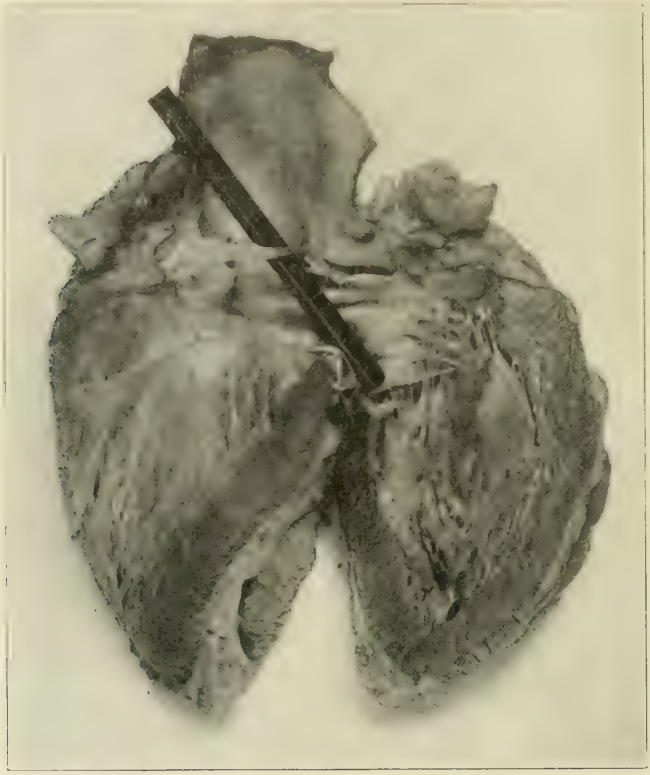
Closely related to these is the condition in a heart from the body of a negro, aged 50, admitted to the Cook County Hospital to the service of Dr. Loeb with a clinical diagnosis of cirrhosis of the liver and ascites. The examination revealed little except the ascites. The heart was normal in its rate, rhythm and sounds; there was no murmur.

He died nine days after entrance from chronic incomplete intestinal obstruction complicated by empyema. (Necropsy by Dr. Singer, resident pathologist.) The heart weighed 202 Gm. The epicardium over the left ventricle was gray and opaque. There was considerable subepicardial fat. The right ventricle was soft and almost completely covered with fat; the left was firm. The surfaces made by cutting the left myocardium were smooth, red, moist and glistening, and the margins were infiltrated with fat. The myocardium of the left ventricle measured 10 mm. at the base, 7 at its middle and 6 at the apex. The surfaces made by cutting the myocardium of the right ventricle were smooth, brown-red, moist and glistening, and the infiltration of fat was greater than in the left. The myocardium was 3 mm. at its base and 2 mm. at the apex. The left ventricular endocardium was smooth, moist and glistening, and the papillary muscles and chordae tendinae were normal. The right endocardium was covered by fatty tissue, and there was a bit of fat about the papillary muscles and chordae tendinae.

The mitral valve ring was 8 cm. in circumference. The posterior leaflet was unchanged. The anterior leaflet was wrinkled, moist and glistening and its free margin was somewhat thickened and firm. The aortic ring was 5 cm.

in circumference. The cusps were normal. A triangular cord crossed the aorta just distal to the leaflets. One end 1.5 cm. wide was attached to the aorta just beyond the right cusp, the other much more tenuous end was attached to the aortic walls just above the common insertion of the posterior and left cusps. The tissue of the cord appeared similar to that of the cusps. The pulmonic ring was 6 cm. in circumference; the leaflets were normal.

The interventricular septum was normal. The aorta was dilated at its base. The lining was smooth and moist. There was a small yellow patch



Heart from a negro, aged 50, showing anomalous band crossing the channel of the aorta just distant to the aortic leaflets; a marker passes under the band.

in the intima 8 by 2 mm. just distal to the mouth of the posterior coronary artery with the intima slightly puckered there. The pulmonary artery was elastic and its lining was smooth, moist and glistening. The walls of the coronary arteries were rather hard, the channels tortuous. Their lining was smooth. The auricles were normally smooth.

Abbott (Osler and McCrae: Modern Medicine, Philadelphia, J. B. Lippincot Company) groups cardiac anomalies thus: (*a*) those due to the arrest of growth at an early stage before the different parts of the heart have been entirely formed, and (*b*) those produced at a later stage by fetal diseases.

The normal appearance of the aorta with this band near its root, together with the normally formed aortic cusps, indicates that the condition in all probability did not arise because of some disease of the fetus in utero, but with the development of the semilunar cusps.

The exact development of the semilunar cusps is not definitely settled to date. It is the present day notion (Tandler, J.: The Development of the Heart, Philadelphia, Keibel and Mall, **2**:534-569, 1912. Humphrey, L.: Congenital Malformations of the Heart, in Allbutt: System of Medicine, London, **6**:697-725, 1898. Rokitansky, C. F.: Die Defekte der Scheidewände des Herzens, Wien., 1875) that they are hollowed out from endocardial thickenings in the transitory bulbus aorta of the embryonic heart.

In this heart it is possible that supernumerary endocardial thickenings formed distal to those from which the aortic leaflets developed and by growing came into contact so as to form a cord instead of hollowing out into accessory cusps.

May 10, 1926.

A CONGENITAL PERFORATE INTERVENTRICULAR SEPTUM OF THE HEART ACCOMPANIED BY A SHORTENED MEDIAL TRICUSPID LEAFLET AND A DILATED PULMONARY ARTERY WITH TWO CUSPS

SEYMOUR WEINSTEIN

From the Pathological Laboratory, Rush Medical College, Chicago

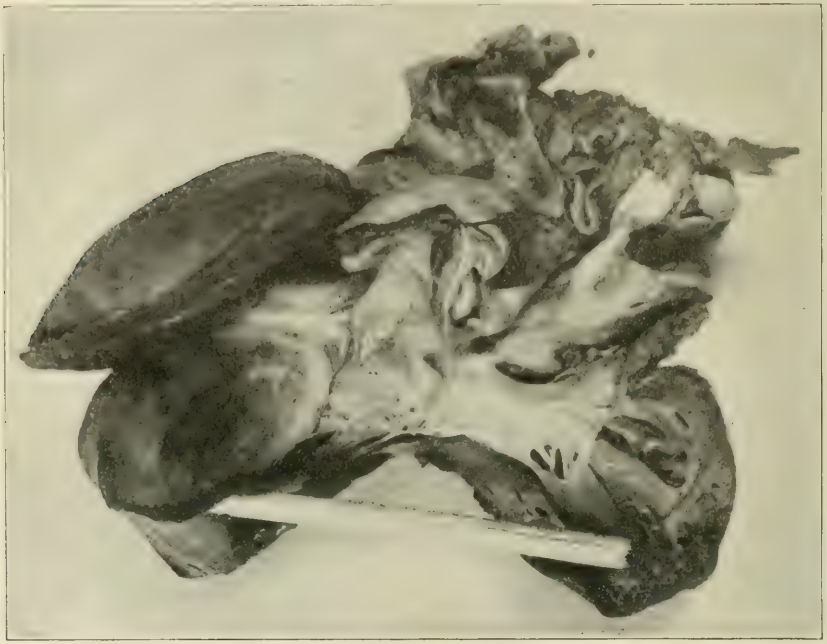
In 1922, Gutzeit (*Virchows Arch. f. path. Anat.* **237**:355-372 [Nov. 22] 1921) described a congenital opening in the membranous portion of the interventricular septum with defects of the tricuspid leaflets. The septal opening was 16 by 11 mm., situated under the posterior and partly under the right aortic cusps. Its margins were fibrous tissue. On the right side it was covered by the combined insertion of the medial and posterior tricuspid leaflets, the medial firmly attached to the fibrous margin of the opening in front and below and the posterior similarly bound behind and below along the margin of the opening in the septum. The upper posterior margin of the opening had no connection with the tricuspid leaflets. Also the medial tricuspid leaflet was narrow and thick, measuring 14 mm. at its distal margin and 13 at its middle and insertion, and at its insertion it had a plexiform trabeculated arrangement. Lying between two trabecular thickenings there was an oval opening, 16 by 3 mm., with a sharply defined margin immediately under the posterior insertion of the medial leaflet exactly opposite the ventricular septum defect.

These leaflets were attached above the annulus fibrosus and formed with the posterior tendinous membrane, which demarcated the septal defect, a pocket 8 mm. deep into which a sound could easily be passed through the defect into the left ventricle.

One of the hearts I have examined is quite like that described by Gutzeit. It is the heart of a child 6 months old admitted to the service of Dr. Bachmann and Dr. Gibson at St. Luke's Hospital, Chicago, with a clinical diagnosis

of bronchopneumonia. Physical examination of the chest failed to disclose anything of interest with reference to the heart. The child died the day after entrance and the necropsy and histologic examinations by Dr. Edwin F. Hirsch confirmed the clinical diagnosis.

The heart weighed 53 Gm. The endocardium, epicardium and surfaces made by cutting were smooth and normal. The myocardium of the left ventricle measured 7 mm. at the apex and middle and 8 at the base. The anterior wall was markedly trabeculated, and the papillary muscles were heavy. The chordae tendinae were normal. The mitral leaflets were smooth and somewhat narrow.



Heart of a 6 months old child showing shortened medial leaflet of the tricuspid valve against the interventricular septum covering a defect in the septum. It may be noted that the papillary muscle of this leaflet is not well developed; also the thickened papillary muscle of the anterior leaflet.

The mitral ring was 4.5 cm. in circumference, the aortic 3. The aortic cusps and lining were smooth and normal.

The right ventricle was markedly trabeculated. The tricuspid ring was 5 cm. in circumference. The myocardium of the right ventricle was 1 mm. at the apex, 5 at its middle and 3 at the base. The posterior and anterior tricuspid leaflets were smooth and normal. The papillary muscle of the anterior leaflet was thick and the chordae tendinae were well developed. The medial leaflet was 8 mm. at its origin and 10 mm. at its free margin. It was brought up somewhat tightly against the defect in the upper part of the interventricular septum. It was trabeculated distally, and between two thickened

fibers on its posterior surface there was a valve opening 2 mm. in diameter. This was directed downward toward the right ventricle. The papillary muscle of this leaflet was rather ill defined and fused with the septum. The chordae tendinae were few and threadlike.

The septum had an opening 8 mm. in diameter below the right and middle aortic cusps, and directed downward and posteriorly into the right ventricle, with a well defined margin of fibrous tissue.

The pulmonic ring was 3.2 cm. in circumference. The pulmonary artery just above the valve was dilated to 3.8 cm. in circumference. Its intima was smooth. The valve had only two cusps, the right much the larger. Both were well formed.

The right auricle was moderately deepened and trabeculated. The left auricle was thin-walled and more or less smooth.

The foramen ovale was present as an oblique opening.

Congenital defects of the tricuspid leaflets are rare, and only a few have been reported. The first report, according to Gutzeit, was that by Reick in which the defect in the tricuspid was so great that the auricle was separated from the ventricle only by a ring-shaped swelling. He also mentions the hearts reported by Ebstein in 1866 in which a sack was suspended into the right ventricle from the cartilaginous bicuspid ring. This had only a lateral insertion in the annulus and went over medially into the endocardium of the septum. The hypertrophied front and back leaflets hung in the sack, and there was only a remnant of the middle. In other reports by Marxsen, MacCallum, Geipel and Schoenenberger the medial leaflet was underdeveloped. In the three hearts described by Heigel the anterior leaflet was most developed and the medial least. The conditions in all these hearts, the anomalies of the tricuspid leaflets, have been due to maldevelopment.

The accounts by Preis and Hart deal with two hearts, each with a perforate interventricular septum and defective development of only the front tricuspid leaflet. In that described by Preis the right ventricular cavity was moderately enlarged; the septal opening was 10 by 12 mm. and bounded below by the septum, above by portions of the back and right aortic leaflets and in front by the aortic septum. The auricular septum failed to meet the ventricular septum behind. This defect reached backward and considerably above the aortic opening up to the middle of the auricular septum. The pars membranacea was absent. The anterior leaflet of the tricuspid valve was considerably lengthened, and the medial leaflet was thickened. The contiguous halves of these leaflets were brought up against the defect by a strong thick band which fixed them against the right margin of the opening.

In Hart's report, the heart was also that of a child who died from pneumonia when 1 year old. The left ventricle was slightly dilated. The great vessels were normal. Immediately under the right aortic cusp there was an oval opening with a slightly thickened margin bounded above by the insertion of the aortic cusps. By transillumination the tissue close about the opening, especially the posterior aortic cusp, was translucent. The defect was in the wall of the right ventricle where the anterior and medial tricuspid leaflets joined. The medial leaflet possessed old knotty thickenings the size of a pinpoint, and there was marked contraction of the chordae tendinae.

It has not been decided how the shortening of the medial tricuspid leaflet occurs, but the development of these leaflets is closely associated with that of the septum between the ventricles.

The internal division of the heart into right and left sides is affected by three septums. These appear within the cavity of the heart perfectly independent of one another. They are the auricular, ventricular and truncus arteriosus septums. The greater part of the ventricular septum is formed from the septum inferius. It is completed above partly by the endocardial cushions at the lower edge of the interauricular septum, the intermediate septum of His and by the prolongation of the aortic septum. The aortic septum grows caudad beyond the truncus arteriosus so as to project a certain distance into the ventricular cavity. It then fuses with the free lower edge of the interauricular septum, while finally the septum inferius extends so as to meet and fuse with the interauricular septum.

In these malformations the membranous septum is wanting and the septum inferius fails to reach and fuse with the septum superius. The presence of other defects and the absence of any evidence of inflammation point definitely to some interference with the normal processes of growth in embryonic life. A bicuspid pulmonic valve is not uncommon, is frequently associated with defects of the interventricular septum and is probably due to a suppression of one of the endocardial cushions. The slight hypertrophy of the wall of the right ventricle is due to the forcing of blood through the opening in the septum into the right ventricle with each systole and the increased work thus thrown on that part of the heart. The anomaly of the medial tricuspid leaflet was probably associated with a leakage, failure of the leaflets to close the tricuspid opening, and brought about the dilatation of the right auricle. An increased volume of blood sent into the pulmonic artery probably caused dilatation of that vessel.

May 10, 1926.

HEALING SPONTANEOUS RUPTURE OF THE POSTERIOR MITRAL PAPILLARY MUSCLE

F. K. POWER

From the Henry Baird Favill Laboratory of St. Luke's Hospital

Spontaneous rupture of a papillary muscle of the heart, according to reports in the literature, is rare. The first account seems to have been made by Courvisart (Diseases of the Heart [transl. by Jacob Gates], 1812, p. 199) who records this disorder in the heart of an adult dying suddenly, and the rupture of a mitral valve papillary muscle was caused by a suppurative inflammation. Bertin (Traite des maladies du coeur et des gros vaisseaux, Paris, 1824, p. 52) reports the traumatic rupture of a papillary muscle which was thought to have resulted from the stress of coughing, although there were vegetations on the chordea tendinae. In a report by Dennig (*Deutsches Arch. f. klin. Med.* **96**:163, 1909), a similar rupture followed severe illness with a thrombosis of the coronary arteries. The report by Heiman (Laennec, R. T. H.: Diseases of the Chest [transl. by John Forbes], 1838, p. 718) is unusual in that a papillary muscle of the tricuspid valve was torn, and he lists an account by Legendre in which a severe blow on the chest caused the rupture of a mitral valve papillary muscle. Wankel (Ein Fall von spontaner Papillarmuskel zerreissung,

I. D. Giessen, 1911) in 1911 described a rupture of the anterior muscle of the mitral valve due to multiple thrombi of the coronary arteries, especially the ramus verticalis of the descending branch of the left coronary artery. Microscopically, there was a necrosis of the papillary muscle stump and a marked fatty degeneration of the myocardium.

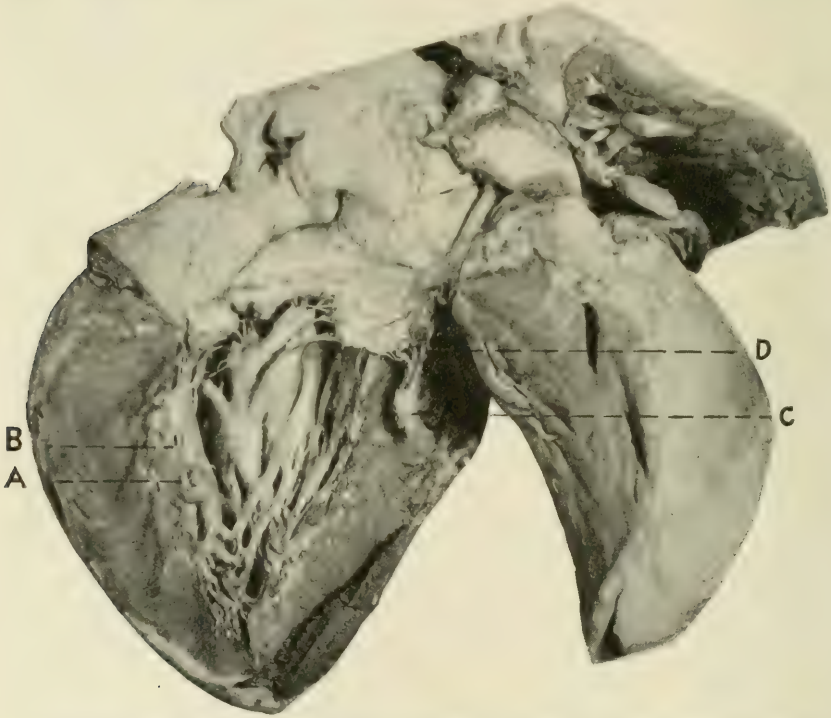
Teacher (*Glasgow M. J.* **75**:374 to 376, 1911) describes the heart of a man, aged 64, whose death occurred suddenly, and postmortem examination demonstrated a left mitral papillary muscle torn off in the middle portion. The edges were frayed and the muscle infiltrated with blood for a short distance on either side of the tear. The edges of the torn surface were curled slightly. In sections of the ruptured end of the papillary muscle, the distal portion was covered with a white thrombus containing a few red blood cells and many leukocytes. There was a marked infiltration with polymorphonuclear leukocytes between the ruptured fibers. Close to the rupture, the fibers were in various stages of degeneration, the cells shrunken, the striations lost and the nuclei absent.

In Spaulding's report (*Bull. Johns Hopkins Hosp.* **32**:30, 1921) of sudden death in a man, aged 31, the heart at the postmortem examination weighed 560 Gm., and the posterior (inferior) papillary muscle of the mitral valve, which was "Y" shaped, was torn in the inferior pillar, close to where the chordae tendinae were attached. The fragment attached to the valve was yellow, the endocardium smooth but opaque. The torn end was rough, irregularly conical in shape, and covered with a firm adherent clot. The center contained muscle which was surrounded by a yellow ring of necrotic tissue just beneath the endocardium. The stump was covered by endocardium. The line of demarcation was sharp and bordered by a zone of hemorrhage. There were petechial hemorrhages of the other papillary muscles. Microscopically the central part of the papillary muscle consisted of necrotic tissue with nuclear fragments, and along the margin of this necrotic region, many leukocytes. Beyond the leukocyte zone the muscle fibers were shrunken, the striae and nuclei absent, and there were small hemorrhages between the atrophied fibers. The muscle cells adjacent contained fat droplets. In Levaditi preparations spirochetes were found just beyond the necrotic region, but the tissue change did not resemble a gumma.

Of these reports, that by Teacher is the only one in which healing of the torn fragment of papillary muscle is recorded, and the healing process in this is presumed to be of not more than a week's duration. The surface of the torn papillary muscle in the heart described in the following report has healed completely.

A. R., a negress, aged 42, was admitted to St. Luke's Hospital, Dec. 3, 1925, to the service of Dr. Robert Preble, complaining of dyspnea, slight edema of the feet and precordial pain for three months. When admitted there was no generalized edema, but the liver was four fingerbreadths below the costal margin, the heart much enlarged, with a systolic murmur heard best over the apex and transmitted to the axilla, appearing to be an old mitral lesion with decompensation. The patient became gradually worse, the dyspnea increased, the extremities became edematous and the edge of the liver descended five fingerbreadths below the costal margin. The temperature recorded was about 100 F. On Jan. 3, 1926, the patient reported a severe heart attack the night

before, with pain in the epigastric region and extreme dyspnea. The heart rate was 106 and very irregular. Morphine gave some relief. The following morning she was resting more comfortably. On January 7, there was some fluid in the right side of the chest, and her general condition seemed better. Following this she gradually became worse, dyspnea increased, and the pulse became irregular. At 3 a. m. on Jan. 12, 1926, the pulse was markedly irregular, the rate 96, respirations 18. At 5:36 the pulse could not be obtained at the wrist, and death followed shortly.



A and *B* indicate mural fragments of the ruptured posterior mitral papillary muscle; *C*, necrotic fragment of the papillary muscle attached to the valve leaflet; *D*, ruptured chordae tendinae.

The Wassermann test of the blood was negative. The blood contained 29.4 mg. of urea nitrogen, 56 mg. of nonprotein nitrogen per hundred cubic centimeters. The urine contained a trace of albumin. No bacteria were found by cultures of the blood.

Necropsy was performed by Dr. Edwin F. Hirsch. The essential changes concerned the heart and those associated with cardiac decompensation. The lower margin of the right lobe of the liver was 4 cm. below the costal arch. There was marked emphysema of the lungs. The amount of pericardial fluid was slightly increased. The heart was 17 cm. obliquely and 12 cm. transversely. The tricuspid ring admitted the tips of five fingers, the mitral of four fingers.

There was marked hypertrophy of the myocardium of the left ventricle; its maximum thickness, midway between the apex and the mitral ring was 3.5 cm. The heart with 40 cm. of the aorta and 3 cm. of the pulmonary vessels weighed 890 Gm. There was a recent embolus occluding the right branch of the pulmonary artery. On the posterior wall of the left ventricle, 5 cm. from the apex of the heart, was a ruptured posterior papillary muscle (*A* in illustration). In this place there was a conical stump, 1.1 cm. in diameter, projecting 1 cm. into the lumen of the ventricle. The tip of the muscle stump contained a circular depression about 7 mm. in diameter and about 1 mm. deep. The center of this region was elevated red-brown tissue, the peripheral edges of which were curled inward overlapping a conical elevation 2 mm. in diameter, and a similar whiter elevation 1 mm. in diameter. On the superior surface of the apex of this fragment of muscle was a tag of white tissue 2 mm. long and 0.5 mm. in diameter. The surface of this fragment of papillary muscle was covered with a smooth, shiny endocardium. Opposite this papillary muscle and attached to the posterior leaflet of the mitral valve by three chordae tendinae, which averaged from 1.3 to 1.8 cm. in length and from 0.5 to 1 mm. in diameter, was another fragment of papillary muscle which seemed to have been torn from the stump described above (*C* in illustration). This fragment was 1.2 cm. long and from 0.3 to 0.5 cm. in its other dimensions. From 4 to 6 mm. of the surface of this fragment was covered by gray, shiny tissue-like endocardium. The remaining distal 0.4 to 0.5 cm. of muscle tissue was whiter, with a roughened surface and a necrotic appearance. The tip was roughened fragments of tissue averaging 0.7 mm. in diameter, from which projected numerous fine, white strands like fibrous tissue. Instead of the healing process evidenced in the other fragment, there appeared to be a necrosis with shrinkage of the tissue of this fragment.

On the right of the conical stump of the papillary muscle and 0.6 cm. above it, was another papillary muscle stump 0.5 cm. long and averaging 0.4 cm. in diameter (*B* in illustration). The apex of this was similar to the one first described, was conical, covered by gray, shiny tissue-like endocardium, and the tip was turned in forming a ring 0.3 cm. in diameter. On the same posterior leaflet of the mitral valve, just to the left, was a chorda tendina, 1.3 cm. long and 0.5 mm. in diameter, which appeared to have been torn from this fragment of papillary muscle (*D* in illustration). The distal tip of this chorda tendina was necrotic, the surface irregularly roughened. There were four shorter fragments of chordae tendinae which seemed to have been torn from the former and averaged from 0.3 to 0.5 cm. in length. The circumference of the tricuspid ring was 12 cm. There was a mural thrombus of the right auricula 4 by 3 by 2 cm. The aortic ring was 6 cm. in circumference. There was a linear wrinkling of the root of the aorta and a slight aneurysmal bulging, the wall of which was thin. In 13 cm. of the thoracic aorta there was a similar linear wrinkling. There was a marked generalized arteriosclerosis. In sections, there was a moderate fibrous myocarditis, and in those of the aorta the intimal side of the media was irregularly roughened and necrotic; the space between was filled with disintegrating cells and blood. Around many of the blood vessels of the adventitia and media, there was a small round cell infiltration, changes like those due to syphilis.

Anatomic Diagnosis: Healed rupture of the posterior papillary muscle of the mitral valve; marked hypertrophy of the myocardium of the left ventricle of the heart; fibrous changes of the anterior mitral leaflet; mural thrombosis of the right auricula; recent embolus of the right branch of the pulmonary artery; acute emphysema of the lungs; syphilitic sclerosis and fatty changes of the aorta; chronic diffuse nephritis (arteriosclerotic kidneys); chronic passive hyperemia of the viscera; fibrous myocarditis; etc.

In all of the reports mentioned except the one by Heiman, the papillary muscles torn are of the mitral valve. In four reports (Bertin, Dennig, Wankel, and Teacher) there was a marked sclerosis of the coronary arteries, and in two (Wankel and Dennig) a thrombosis of the coronary arteries. Courvisart makes no mention of either condition, and in Legendre's report the coronary arteries were normal. In one (Bertin) the chordae tendinae were covered with vegetations. Syphilis seems to have been the cause in the report by Spaulding. In no instance has death occurred immediately at the time of rupture but hours or days later, and usually because of some secondary factor.

There seems to be no other report of complete healing of a torn papillary muscle. This is a distinctive feature of the heart described here. Careful examination of the coronary arteries in this heart demonstrated a marked sclerosis but no thrombosis. The etiology of the rupture is therefore obscure but it may be syphilitic.

Spontaneous rupture of the papillary muscles of the heart is rare. When it occurs the lesion usually is of the mitral valve. Death usually follows some time after the accident. There is no one etiologic factor, nor are there definite symptoms.

May 10, 1926.

MALIGNANT TUMOR OF THE THYMUS WITH EXTENSIVE METASTASES

SETH E. BROWN

A man, aged 36, was admitted to the Research Hospital of the University of Illinois with the diagnosis of carcinoma of the thyroid gland and mediastinal tumor. The patient's condition became progressively worse, and he died five months after the onset of the first symptoms.

Postmortem examination by Dr. R. H. Jaffé demonstrated a large tumor mass in the anterior superior mediastinum with metastases to the lungs, heart, thyroid gland, cervical glands, liver, pancreas, kidneys, suprarenals and mesenteric lymph glands.

Microscopically, the primary growth contained much hyalinized fibrous tissue with few tumor cells, while the metastases were cellular. The cells varied greatly in size and shape, the nuclei were large and vesicular, and fine protoplasmic branches extended from cell to cell. In places the cells were arranged about minute alveoli. No Hassall's corpuscles were found. The tumor is diagnosed as reticulum cell lymphosarcoma.

DISCUSSION

R. H. JAFFÉ: The tumor demonstrated by Dr. Brown shows how difficult it sometimes may be to determine whether a tumor is sarcoma or carcinoma. All the histologic criteria characteristic of sarcoma or carcinoma are of no value with a tumor composed of immature cells. In the metastases to the lymph vessels of the lung, to the alveoli of the lung and to the vesicles of the thyroid, tumor cell borders on tumor cell, and there is no fibrillar reticulum demonstrable. In the places, however, where the cells break into the stroma, they mingle so intimately with the latter that most of the cells are embedded in a network of fibrils. Occasionally, especially in the pancreas, there are small alveoli without intercellular fibrils (Bielschowski's stain). When we call the tumor a reticulum cell lymphosarcoma we do so on account of the branched shape of the cells forming a protoplasmatic reticulum besides the fibrillar one. This protoplasmatic reticulum also is present in the alveoli. In the periphery of the alveoli the protoplasmatic branches joint the fibrillar structures.

The term thymoma should be restricted to the tumors of the thymic region of undoubtedly epithelial origin containing Hassall's corpuscles.

May 10, 1926.

SKIN REACTIONS WITH GONOCOCCUS TOXIN

RUSSELL D. HERROLD

(John McCormick Institute for Infectious Diseases

Positive skin reactions with gonococcus culture filtrates were reported with dilution 1:100 and less. Recently, reactions have been noted with various filtrates in dilutions 1:500 and 1:1,000. Ordinary broth is the medium with the exception of the addition of 0.1 per cent dextrose and the substitution of 0.1 per cent dibasic sodium phosphate for the sodium chloride.

The cultures were made in large flat bottles containing broth to a depth of about 1 cm. The bacteria grew abundantly and at the end of seven days the cultures were filtered through Berkefeld N filters. Subcultures of the seven day growth demonstrated that the gonococci were viable.

Gonococci grown on solid medium and then added to broth were set aside for seven days in order to autolyze. This control broth was filtered and skin tests made. No reactions were found in any instance with a dilution of 1:500, and but few with a dilution of 1:100. A comparison by stains of the amount of autolysis of the two types of gonococcus antigen indicated that the amount of autolysis was about the same. These results seem to indicate that there is a toxin produced by the growth of the gonococcus in this medium which differs from that due to autolysis.

Skin tests have been made in children and adults with gonorrhea. Skin reactions are negative or reduced in intensity after a series of subcutaneous injections of the gonococcus toxin. Frequently there is a reduction in the intensity of reaction after a cure. Patients with persistent strongly positive

reactions after the clinical symptoms have subsided seem more likely to have later exacerbations of gonorrhea, and thus the test may be of value in the determination of latent infections. The serums of patients receiving a series of subcutaneous injections of the toxin contain some antitoxic substance, as indicated by the neutralization tests. The injection of the toxin subcutaneously seems to decrease the susceptibility toward infection. However, the number of observations is too limited for final conclusions.

May 10, 1926.

TRANSACTIONS OF THE CHICAGO PATHOLOGICAL SOCIETY

VOL. XII JUNE 1, 1927 NO. 5

ADAMANTINE EPITHELIOMA

WARNER S. BUMP

Henry Bayd Favill Laboratory of St. Luke's Hospital, Chicago

This is a report of two adamantine epitheliomas and an account of Malassez' explanation of the origin of these tumors.

The enamel of the tooth is the product of a glandlike structure, the enamel organ, which is derived from an infolding of the buccal epithelium. The enamel organ proper is the result of intensive epithelial proliferation; only a few cells actually taking part in enamel secretion. After the crown is entirely formed, none of the epithelial structures has any function in man, and they remain only as isolated groups of characterless cells about the roots of teeth. In animals with numerous dentitions the epithelium remains active, forming enamel for the teeth of the various dentitions.

It is Malassez' idea that these atrophied cells may be stimulated to new growth by infection or trauma, forming tumors, the structure of which resembles the epithelial formations from which the proliferating débris is derived. He thus explains how these tumors may be solid or cystic with cells varying from squamous to cylindric or star-shaped.

The first tumor of the report was practically solid, occurring in the right side of the upper jaw of a man, aged 50, following the formation of an alveolar abscess present for eight years before treatment, and recurring three years after removal by the curet and electrocautery. It contained enameloblast-like cylindric cells and star cells, arranged much as in the enamel organ. The second tumor was infected, appearing in the left side of the lower jaw of a woman, aged 22, following the removal of an impacted third molar and present for two and one-half years before operation. It contained epithelial masses of squamous, cuboid and star-shaped cells.

From the reports of forty-eight observers it is found that fifty-three of sixty-nine tumors were in the lower jaw, fourteen in the upper jaw and two in both jaws. Thirty-two of fifty-five tumors were in women. The oldest patient was 75 years old, the youngest 8. The average age at which the tumors were first noticed was at 35.5 years. The average period of growth was 5.4 years.

Adamantine epitheliomas grow within alveolar borders, distending the bone, sometimes breaking through the bony shell into the maxillary sinus, orbit or even into the cranial cavity; but they do not spread by metastasis. However, if they are not completely removed at the first operation, they recur persistently.

(A complete report is published in *Surgery, Gynecology and Obstetrics* **44:** 173, 1927.)

October 11, 1926.

THE PURIFICATION OF DIPHTHERIA ANTITOXIN

EDNA RUTH MAIN

Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago

This report includes the results of investigations which Dr. A. P. Locke and I have been making. Immune serums, such as diphtheria antitoxin, are extremely variable and impure preparations of the desired therapeutic substance. The potency of diphtheria antitoxin varies from 200 to 2,000 units per cubic centimeter. Its protein content varies from 6 to 12 per cent. The protective capacity per unit varies from a maximum value characteristic of fresh, highly avid serums, to a minimum value characteristic of aged and heated serums.

While it is necessary to protect a diphtheria patient against only a small amount of continuously introduced toxin, the unit effectiveness of the antitoxins now available is so low and the rate of absorption from the customary intramuscular injections so slow that relatively enormous doses must be administered to secure complete protection. For this reason, diphtheria antitoxin is almost universally subjected to concentration procedures since the injection of large fluid volumes or large amounts of foreign protein is not considered advisable.

Antitoxin is associated, mainly, with the pseudoglobulin fraction of the immune serum. This fraction constitutes less than 40 per cent of the total protein present, and various salt precipitation and electro-osmotic methods have been devised for the purpose of separating it from the other, undesirable proteins. These methods accomplish a concentration of about 500 per cent, and the concentrated preparations are in every way as effective as the raw serums and are much less active in causing serum sickness.

A greatly increased quantity of undesirable proteins can be precipitated from immune serums if these are first heated for some time at 60 C. Although a somewhat greater concentration is thus obtained, the unit effectiveness is so greatly reduced that the advisability of this procedure may be questioned.

Any separation of only from 60 to 80 per cent of associated serum proteins from a serum which contains less than 0.1 per cent of antitoxic protein does not greatly purify it. The residual preparation may still be less than 5 per cent pure.

A much higher degree of concentration has been obtained with immune serums of an anticellular nature, such as typhoid, meningococcus and pneumococcus agglutinins, and antisheep hemolysin. Rabbit antisheep hemolysin has been concentrated in our laboratory by a method of specific adsorption somewhat as follows: Fresh rabbit antisheep amboceptor serum is added to the antigenic red cells in such concentration that 90 per cent of the potency is absorbed. The hemolysin saturated cells are laked by the complement present and are centrifugalized and washed until comparatively free from adhering serum. The combining power of the cell stroma is then modified by extraction with ether, and the desorbed antibodies are recovered by suspension in a slightly acid solution. These solutions are of varying purity and avidity

depending on the avidity of the original amboceptor serum. The best preparations contain 0.000,000,007 Gm. of nitrogen per hemolytic unit, and represent a concentration of 150,000 per cent.

These values, so far in advance of those obtained in the nonspecific fractionation of diphtheria antitoxin, seem to indicate that this antiserum might be purified more successfully by a method of specific adsorption on its antigen, diphtheria toxin.

Several difficulties attend this application. Diphtheria toxin, unlike erythrocytes or bacteria, is a soluble substance. It is so toxic that the immunization procedure is necessarily long drawn out. The serum produced is poorly avid and combines only slowly and loosely with toxin. It was not until 1920 that Nicolle observed that mixtures of diphtheria toxin and antitoxin precipitate

Comparison of Degree of Concentration of Diphtheria Antitoxin Obtainable by Different Methods

	Mg. of Nitrogen Associated With One Unit	Degree of Concentration: Mg. of Nitrogen per Unit Original Serum / Mg. of Nitrogen per Unit Final Preparation
	(Approximately)	(Approximately)
Untreated plasma	0.007–0.07	1
Early salt precipitation methods, "insolubilization," nonspecific adsorption	0.016–0.02	2–3
Improved salt precipitation methods, electrodialysis	0.013	3–5
Iso-electric precipitation	0.003	12–15
Specific precipitation with diphtheria toxin: solutions of the precipitate		
1. According to Ramon	0.0025	15–20
2. With ether extraction	0.0020	18–25
3. With electrodialysis	0.0013	30–40
Extracts of the precipitate (iso-electric precipitation)	0.0005	60–100

within a narrow range of concentration ratios. This observation was confirmed and extended by Ramon to include a method of titrating these substances in vitro.

Two cubic centimeters of a potent, fresh diphtheria toxin is measured into a series of micro test tubes. To these are added graded portions of the antitoxin. After standing for some time, floccules are observed in one of the tubes and, shortly after, in the contiguous ones. The first flocculating tube is found to contain a nearly neutral mixture of toxin and antitoxin.

Ramon analyzed the floccules and found them to contain three fourths of the total toxin and antitoxin of the original mixture, associated with less than 4 per cent of its nitrogenous constituents.

The floccules are not, however, a pure compound of toxin and antitoxin. They contain varying amounts of associated proteins, lipids and even inorganic salts. We have subjected them to ether extraction, electrodialysis and iso-electric fractionation, with the result shown in the table. Iso-electric fractionation has given the purest final preparation and is, at the same time, least injurious to the intrinsic avidity of the preparation. However, the largest

single factor in influencing the purity of the final preparation is the avidity of the toxin for the antitoxin in the original flocculation mixture. Work is now in progress on the production of more avid raw materials, and we hope soon to obtain a purification of diphtheria antitoxin comparable to that already obtained with hemolysin.

The procedure of fractionation used is somewhat as follows: A mixture of toxin and antitoxin identical in composition to that in the first flocculating tube of the preliminary titration is allowed to stand until well formed floccules have separated and the supernatant liquid is brilliantly clear. After centrifugalization this supernatant is removed and the sediment washed five times with physiologic sodium chloride solution and twice with distilled water. A solution of this washed residue in dilute acid may then be heated, ether-extracted or electrodialyzed to destroy the combining power of the contained toxin. These procedures greatly increase the yield of recovered antitoxin but are injurious to the avidity. Iso-electric fractionation, on the contrary, gives small yields of superior purity and avidity. The best preparation thus far obtained contains 0.000,003 Gm. of protein per antitoxic unit and represents a concentration of 10,000 per cent.

DISCUSSION

E. Pribram: It is important theoretically as well as practically to know whether the purified antitoxin has the same curative effect as the original antitoxic serum. The proper concentration not only increases the amount of units and their ratio to the protein content, but also avoids serum sickness. I try to purify the serum, also to avoid the anaphylactic shock after a previous serum injection. In these respects, all attempts with different methods have been fruitless.

For the commercial use of the iso-electric method it would be necessary to know exactly the absolute loss of antitoxin units. The absolute loss of antitoxin units usually increases with the removal of proteins (purification). Losses were higher by using electro-osmosis than by using precipitation with salts. The high expense of serum concentration demands economic methods.

D. J. Davis: Can the method be used for the commercial production of antitoxin?

A. P. Locke: The comparative therapeutic usefulness of fresh and concentrated diphtheria antitoxin preparations is, indeed, an important question. Methods of antitoxin concentration which include prolonged heatings at 56 to 60 C. may decidedly reduce the effectiveness, per unit, of the original serum.

The purification of diphtheria antitoxin by selective adsorption on the toxin and consequent fractionation of the separated floccules does not, at this time, seem adapted to commercial, large-scale production.

E. F. Hirsch: The purification of immune serum seeks to eliminate serum sickness. Purified hemolysins prepared from dog and rabbit serums, and the purified diphtheria antitoxins from horse serum have sensitized guinea-pigs specifically. The hope of eliminating serum sickness seems to lie in concentrating the therapeutic dose in a quantity of protein too small in a sensitive patient to cause symptoms.

October 11, 1926.

PRIMARY SCLEROSIS OF THE PULMONARY ARTERY AND ITS BRANCHES *

CHARLES M. BACON
AND
CARL W. APFELBACH
CHICAGO

Primary or genuine sclerosis of the pulmonary artery and Ayerza's disease are two clinical entities which have been studied with increasing frequency during the last twenty-five years. Even though diminution of the pulmonary artery bed by sclerosis of the pulmonary artery and its branches is the essential morbid alteration ascribed to both of these diseases, the clinical manifestations, as described by their exponents, are in many respects dissimilar. Most authors describe syphilitic arteritis of the pulmonary artery in Ayerza's disease, whereas in the other disease syphilis generally has been excluded and another single common etiologic factor has not been found.

PRIMARY SCLEROSIS OF THE PULMONARY ARTERY AND ITS BRANCHES

Posselt [1] was the first to summarize definitely the clinical characteristics of primary sclerosis of the pulmonary artery and to review its literature. Eppinger and Wagner [2] in 1920 emphasized the chief clinical manifestations in reporting five cases, in three of which the correct diagnosis was made before death. These authors collected sixteen cases, the first being by Crudeli in 1870. Posselt [3] again reviewed the literature in 1925, and again defined its clinical and anatomic features. In addition to these reports there are others by H. Schütte,[4] H. R. Miller,[5] H. Liebig,[6] O. Meyer [7] and Löwenstein.[8]

---

* From the Pathological Laboratories of Rush Medical College of the University of Chicago and the Presbyterian Hospital.

1. Posselt, A.: Die klinische Diagnose der Pulmonalarteriosklerose, Samml. klin. Vortr., no. 504-507, 1908. Die Erkrankungen der Lungenschlagader, Ergebn. d. allg. Pathol. u. path. Anat. **13**:298, 1909.

2. Eppinger, H., and Wagner, R.: Zur Pathologie der Lunge, Wien. Arch. f. inn. Med. **1**:83-118, 1920.

3. Posselt, A.: Zur Pathologie und Klinik der primaren Atherosklerosis pulmonalis, Wien. Arch. f. inn. Med. **11**:357-398, 1925.

4. Schütte, H.: Rechtseitige Herzhypertrophie, hervorgerufen durch entzündliche Veränderung der kleinen Lungenarterien, Centralbl. f. allg. Pathol. u. path. Anat. **25**:483, 1914.

5. Miller, H. R.: Sclerosis of the Pulmonary Artery and Its Branches, M. Clin. N. Amer. **9**:670-716, 1925.

(See Footnotes 6, 7 and 8 on following page)

Morbid Anatomy.—The most conspicuous gross change found at postmortem examinations is hypertrophy of the wall of the right ventricle, unassociated with the cardiac and pulmonary diseases[9] that are known to obstruct the pulmonary circulation. Death is usually caused by cardiac decompensation, with edema and marked alterations of the liver, spleen and kidneys, due to long continued passive hyperemia. The lungs are relatively bloodless and small. The wall of the left ventricle is atrophied, and the cavity of the left auricle is small. The gross alterations in the intima of the main portions of the pulmonary artery, mainly fatty change and its sequences, are usually slight in comparison to the changes in the pulmonary arterioles. Tortuosity of the smaller arteries (from 1 to 3 mm. in diameter) has been observed. The pulmonary veins are usually unaltered, but in some instances they are smaller than normal (Hart,[10] Watjen[11] and Posselt).

Microscopic examination of the lungs reveals the cause of the hypertrophy of the wall of the right ventricle, a marked lessening of the channels of the arterioles and small arteries throughout both lungs. Within the middle muscular and subintimal coats there are thick layers of fibrous tissue and usually retrogressive changes, such as hyaline degeneration, vacuolization and lipoid deposits. In the arterioles the elastic tissue of intima is sparse, but in the arteries with a diameter greater than 0.5 mm. there are varying degrees of hyperplasia of the elastic tissue of the intima is sparse, but in the arteries with a diameter infiltrations in the arterial walls, but in most instances inflammatory changes are not observed.

---

6. Liebig, H.: Ueber die primäre Pulmonalsklerose, Zetnralbl. f. Herzkrankh. **18**:45-56, 1926.

7. Meyer, O.: Zwei Fälle von Pulmonalsklerose, München. med. Wchnschr. **72**:1948, 1925.

8. Löwenstein, L.: Ueber Thromboarteritis pulmonalis, Frankfurt, Ztschr. f. Path. **27**:226-236, 1922.

9. The usual or known causes for hypertrophy of the wall of the right ventricle are hypertrophic emphysema of the lungs, mitral stenosis and other valvular and myocardial diseases of the left side of the heart, extensive obliteration of the pleural cavities by fibrous adhesions, fibroid tuberculosis of the lungs, pneumoconiosis, chronic bronchitis and compensatory emphysema (when bronchial asthma existed during life), extensive bronchiectasis, deformities of the thoracic wall and congenital malformations of the pulmonary artery and its orifice.

10. Hart: Ueber die isolierte Sklerose der Pulmonalarterie, Berl. klin. Wchnschr. **12**:304, 1916.

11. Watjen: Isolierte Sklerose der Pulmonalarterie im jüngsten Kindesalter, Deutsche med. Wchnschr. **22**:713, 1924.

Clinical Symptoms.—The patients present the problem of determining the cause for enlargement of the right side of the heart. Mitral stenosis has been the most common diagnosis. Cyanosis is generally present and more marked than is consistent with other signs of myocardial insufficiency, especially shortness of breath. Edema, although it usually appears late in the disease, is more prominent than shortness of breath. Other characteristics described by Posselt and Eppinger and Wagner are as follows: the lung fields in roentgenograms are clear, and the outline of the left auricle indicates that this cavity is not enlarged; physical or roentgen-ray examinations do not reveal evidence of an adequate cause for enlargement of the right side of the heart; the systolic and pulse pressures are usually low, and the second pulmonic sound is accentuated. Posselt believes the noteworthy features possess the following order of importance: cyanosis; hypertrophy of the walls of the right heart chambers; small left auricle; absence of evidence of passive hyperemia of the lungs, and the disproportion between the cyanosis and dyspnea. The disease is one of early adult life or early middle age.

AYERZA'S DISEASE

The second disease attributed to sclerosis of the pulmonary artery is named after Abel Ayerza, who described it in 1901 as "cardiacos negros." Arrillaga,[12] an associate of Ayerza, continued its study and, with others,[13] has described the clinical and anatomic characteristics. Its main features are polycythemia, marked cyanosis and hypertrophy of the wall of the right ventricle.

Morbid Anatomy.—With the hypertrophy of the wall of the right ventricle there is dilatation of the pulmonary artery in its first portion and main branches, with frequently a true aneurysm near the bifurcation and plaques in the main branches and middle-sized arteries. In the main branches there is hyperplasia of the elastic fibers in the media. In the medium-sized branches there is a panarteritis with intense reaction in the intima. The most marked changes in the smaller branches are in the media, where there is splitting of the elastic fibers and hyperplasia of the internal elastic membrane. Many of the patients have had a clinical history of bronchitis and pneumonia. Arrillaga maintains that

12. Arrillaga, F. C.: Early Diagnosis of Pulmonary Arteritis, Rev. Soc. de med. int. **1**:478-483, 1925. Arrillaga, Tobias and Cabred: Sclerose de l'artere pulmonaire, Rev. Asoc. med. argent. **37**:100-113, 1924.

13. Escudero, P.: Polycythemia and Erythrosis with Sclerosis of the Pulmonary Artery, Rev. Soc. de med. int. **1**:463-470, 1925. Ayerza, L.: Ayerza's Disease, Rev. Soc. de med. int. **6**:73-83, 1925. Warthin, A. S.: A Case of Ayerza's Disease, Tr. A. Am. Phys. **34**:219-239, 1919.

histologic evidence of syphilitic bronchitis and pneumonia is present in some bodies, and in others, that there are bands of fibrous tissue in the lungs that increase proportionately as the arteritis diminishes the lumens.

Clinical Features.—Dyspnea is always marked and exists for a long time before symptoms of myocardial insufficiency develop. Cyanosis is so characteristic that the disease was first named "black cardiacs." Polycythemia is usually present. Death is preceded by edema and passive hyperemia of the lungs, rupture of the pulmonary artery, thrombosis or bronchopneumonia.

Arrillaga[12] maintains that sclerosis of the pulmonary artery may be diagnosed even when complicated by emphysema, chronic bronchitis, bronchiectasis and mitral stenosis. He believes that the sclerosis of the pulmonary arteries is always primary and syphilitic, and that it may be complicated by the mentioned pulmonary and valvular diseases, the latter only predisposing the arteries to the syphilitic inflammation.

Warthin[14] emphasized polycythemia in his report, and suggests that many of the forms of polycythemia reported in the literature may be due to sclerosis of the pulmonary artery. He supports the views of Arrillaga and Escudero regarding the syphilitic nature of the changes in the pulmonary artery and accepts Ayerza's disease as a clinical and anatomic entity. He also states in regard to the etiology that: "the lesions in the pulmonary vessels may be secondary to chronic pulmonary disease, bronchitis, tuberculosis, pleural adhesions or any condition producing a final emphysema; or it may be the result of slow infections, as syphilis or malaria, or the result of intoxications."

The case we will report resembles the disease described by Posselt and Eppinger and Wagner, and differs in many clinical and anatomic features from Ayerza's disease. We, therefore, have chosen the name employed by Posselt, namely, primary sclerosis of the pulmonary artery.

REPORT OF CASE

Clinical History.—M. K., a woman, aged 40, married, entered the Presbyterian Hospital, Chicago, Aug. 17, 1926, as a patient of Dr. Charles M. Bacon, complaining of shortness of breath, pain in the chest, loss of weight and a nonproductive cough. She thought that her illness followed an acute pulmonary infection in 1918, during the influenza epidemic. Until 1921, loss of weight and strength prevailed, but then shortness of breath began to appear at intervals. During February, March and April of 1922, there was thoracic pain on exertion severe enough that the patient "would have to stop walking." In 1922 there were: relative dulness in the right posterior axillary line from the fifth to the

14. Warthin (footnote 13, third reference).

tenth ribs with diminished breath sounds; diminished breath sounds close to the spine on the left side from the fourth to the sixth ribs; no enlargement of the heart to the left; no murmurs; the first sound at the apex sharp and ringing; the hemoglobin content, 70 per cent; red blood cells, 3,980,000; white blood cells, 4,500. A roentgenogram demonstrated enlargement of the heart to the right and calcification in the lung fields. The heart beat after exertion was 100 per minute, three minutes later 100. Digitalis gave some relief. A trace of albumin was found in the urine. The weight was 98 pounds (44.5 Kg.). At this time a tentative diagnosis of pulmonary tuberculosis was made.

In March, 1925, the patient weighed 99 pounds (45 Kg.); the heart rate was 90, the respiratory symptoms were improved; the hemoglobin content was 78 per cent; red blood cells, 4,610,000; white blood cells, 4,500.

During the summer of 1925, she was hardly strong enough to walk. The cough, intermittent before and nonproductive, was now paroxysmal and exhausting, with a mucopurulent yellow sputum.

From questions at the time of admission it was evident that there had been cyanosis of the fingers and feet for five years, and that recently the hands "became blue whenever they hung down." For the last year she had also noticed abdominal distress which occurred immediately after eating solid food and which was relieved by belching; vomiting, diarrhea, constipation, hemoptysis or melena had not been present, but excessive flatus had been noted. In January, 1926, swelling of the feet occurred for the first time, for four months it receded and returned several times, but during the last four months before examination it was constant. The cramplike pain in the chest was absent from 1922 to 1926. The only neurologic disturbances were four attacks of headache, each lasting about three days, localized to the right eye and temple and associated with nausea and insomnia.

The patient had been married for twenty-five years, but had never been pregnant. Menstruation was regular, with a twenty-six day interval and a duration of six days, until March, 1926, when the flow decreased and then ceased in June.

There was a severe attack of rheumatic fever during the eighth year but no recurrence. During the last several years she had "rheumatic pains" in various joints intermittently, unassociated with swelling or heat. A goiter developed at puberty, but disappeared in four years. A history of childhood or venereal diseases was not obtained. Her father was living and well; her mother had died at the age of 45 of apoplexy; two brothers were living and well. The patient did not use alcohol, tobacco, coffee or tea.

Report was made as follows after physical examination on Aug. 17, 1926: "Patient is thin, middle-aged, slightly dyspnoeic, and the lips are blue. Hearing is normal. There is no nasal obstruction or puffiness of the eyelids. The sclerae and conjunctivae are unchanged. The pupils react to light and accommodation. The tongue is rough, deeply furrowed and red. There is slight pyorrhea at the upper incisors. The pharynx and tonsils are not acutely inflamed. The thyroid gland is not enlarged. There are a few palpable lymph glands in the anterior cervical chain. The large vessels have no visible pulsations.

"The chest is thin, symmetrical in front. There is slight dorsal scoliosis. Expansion of the chest is fairly good, but excursion at bases only 2 cm. The chest is slightly hyperresonant. There are no abnormal breath sounds or dulness. The apex beat is barely felt, not localized and 100 per minute. The right heart border is 1 cm. beyond the sternal border in the fourth interspace, the left

heart border 8.5 cm. from the midsternal line in the fourth and fifth interspaces. The heart tones are clear, the second tone at the left sternal margin at the base is split, the first sound at the apex rough. There is a systolic murmur heard at the lower border of the heart from the apex to the xyphoid process, loudest at the xyphoid. There are no irregularities. Blood pressure is 105 systolic and 60 diastolic in the sitting position.

"The abdomen is symmetrical and somewhat doughy. There is moderate tenderness in the epigastrium and left hypochondrium. The liver margin is 3 cm. below the costal margin in the right mid-clavicular line. The spleen is not palpable.

"There is edema of the subcutaneous tissues of the legs as high as the knees. There are a few varicose veins. The fingers are not clubbed. When the hands hang down, the fingers become deeply cyanosed.

"The vaginal canal is narrow and short. The body of the uterus is not palpable. A firm mass is palpated through the posterior fornix.

"August 19. The radial pulse is regular, 100 per minute, and small volume. The hands and feet are cold. There is tenderness in the epigastrium and resistance to firm pressure (liver). The edema is diminished.

"August 22. There are coughing spells with pain in the lower part of the chest. Fine crepitant inspiratory râles are heard at the bases. Edema of legs has almost disappeared.

"August 25. There is pain between shoulder blades, lumbar region and lower end of sternum. The lungs are clear. The temperature reached 101 F. No change found in cardiac findings."

During the last two days before death she continued to complain of pain between shoulders; cyanosis increased. Death was rather sudden, with nausea, faintness and cyanosis preceding it a few hours.

On August 17 the hemoglobin content was 85 per cent (Dare); red blood cells, 6,080,000; white blood cells, 7,000. The urine contained a slight amount of serum albumin in all tests; occasional hyaline casts were found; red blood cells were not present; the specific gravity was between 1.008 and 1.015. The blood urea nitrogen was 17.7 mg. per hundred cubic centimeters, creatinine 1.34. Blood was not found in the stools. A Wassermann test was not made.

The temperature was subnormal except on August 25 and 26, when it reached 102 F.

Electrocardiogram: "Rate 100; right heart preponderance; no arhythmia; T-wave inverted in leads II and III (the latter attributed to overdigitalization or myocardial degeneration)."

On August 20, Dr. E. E. Irons made the following observations in addition to confirming those previously mentioned: "maximum left heart border 10 cm. from midsternal line; spleen not palpable; no pulsations in liver; heart dulness shifts on change of position of patient; no thrill palpable at apex; systolic murmur at the apex and to the left of it, and over lower end of sternum a systolic murmur of like character; a short presystolic rough murmur at apex terminating in a sharp first sound; pulmonic second much accentuated; lung resonance and breath sounds are normal; color of patient this morning is normal; pulse regular, but very small volume; rate 90."

Clinical diagnosis: Mitral disease with small heart. "Although there is no thrill and no pronounced typical presystolic murmur, the enlargement of the

right heart and liver, dyspnoea, subcutaneous edema, short presystolic murmur (with heart beating 80 to 90), and accentuated second pulmonic suggest mitral 'narrowing'." Death occurred on August 26.

Postmortem Examination.—Anatomic diagnosis: sclerosis of the pulmonary artery and its branches; hypertrophy of the wall of the right ventrical; edema of the myocardium; fibrous obliteration of the pericardial sac; marked general passive hyperemia; slight ascites; edema of the loose retroperitoneal tissues, gastrohepatic ligament and wall of the gallbladder; indurative shortening of the mesentery and mesocolon (chronic passive hyperemia); moderate emaciation; slight generalized jaundice; cyanotic atrophy of the liver; atrophic emphysema of the lungs; scars of the apexes of the lungs; localized bilateral fibrous pleuritis; localized fibrous perisplenitis and perihepatitis; moderate sclerosis and fatty changes of the aorta; slight coal-pigmentation of the lungs and tracheobronchial lymph glands; slight canities; cysts of the ovaries; bilateral hydrosalpinx; corset constrictions (three) of the liver; vaccination scars (three) of the right arm; tongue shaped left lobe of the liver; fetal lobation markings of the kidneys.

The body was that of a white woman, aged 40, weighing 86 pounds (39 Kg.) and by actual measurement 167 cm. long. The scalp hair was dark brown, slightly tinged with gray. The sclerae were light yellow. The superficial veins of the face and neck, lower extremities and lower part of the trunk were engorged with blood and very prominent. The body nourishment was fair. The neck was long and the front lower portion full. The junction of the neck with the shoulders was almost a right angle. Edema of the subcutaneous tissues was not observed. The breasts were small, the areolae pigmented dark brown. Body heat was present and rigor mortis had not yet developed in the extremities. The thorax was narrow from front to back.

The subcutaneous fat in the midline of the trunk in front was orange-yellow and from 5 to 7 mm. thick. There was about 205 Gm. of brown watery fluid in the peritoneal cavity. Strandlike fibrous adhesions were observed between the spleen and diaphragm. The retroperitoneal tissues were slightly fluctuant. The splenic and hepatic flexures of the colon were not pronounced, the course of the colon being semicircular. The mesocolon everywhere averaged about 10 cm. long. The diaphragm on the right side extended up to the fourth rib, on the left side to the middle of the fifth rib. The loops of the small bowel were reddish purple and collapsed. The lower margin of the liver on the right side was about 1 cm. above the costal margin. The lower margin of the left lobe was narrow and tongue shaped, and it extended 9 cm. caudad to the tip of the xiphoid process. The lower pole of the spleen was about 4 cm. above the costal margin.

The costal cartilages were soft. The lungs did not collapse when the chest was opened. Multiple firm threadlike fibrous adhesions were present between the lungs and the chest wall posteriorly at the lower lobes, and at the apex of the right lung. The maximum transverse diameter of the heart was 14.5 cm. The pericardial cavity was almost entirely obliterated by fibrous adhesions. The main branches of the pulmonary arteries were not obstructed. The blood in the right heart chambers was dark red, almost black, fluid and abundant. The blood did not clot readily when it left the vessels. The medial surface of the left lung was adherent to the pericardial sac by a few fibrous strands.

There was only adipose tissue in the thymic body. The thyroid gland was about twice the normal size, symmetrical and pale brown-purple, and in surface made by sectioning there was an abundance of colloid material and clumps of old fibrous tissue in irregular regions from 2 to 6 mm. in diameter.

In the lining of the aorta there were bright yellowish orange, irregular elevations and some that were gray, involving about one half of the thoracic portion and three fourths of the abdominal portion. Transverse superficial ridges were present in the lining of the renal arteries. The lining of the inferior vena cava, iliac or renal veins was unchanged. The loose retroperitoneal tissues were gelatinous and greenish yellow from the fluid in them.

The cortices of the suprarenal glands were mottled orange-yellow and red. The kidneys were about the normal shape. Surfaces made by sectioning were purple; the medulla was much darker than the cortex, and a moderate amount of bloody fluid appeared on the surfaces. The cortical markings were distinct. Noteworthy changes had not occurred in the renal pelves or ureters.

The lining of the esophagus was smooth and light gray purple. The tracheobronchial lymph glands were dark purple to black and formed a soft mass caudad to the bifurcation of the trachea, triangular and each side about 5 cm. long. Surfaces made by sectioning were moist and dark purple.

In the main portion of the pulmonary artery and the main branches there were bright yellowish orange plaques, involving about one third of the lining.

Stringy fibrous adhesions were seen between the diaphragmatic surface of the right lung and the diaphragm. The right lung weighed 215 Gm., the left 175 Gm.

A yellow, watery fluid was present in the fibrous adhesions in the pericardial sac at the base. The heart with the pericardial sac, but with most of the extrapericardial adipose tissue removed, weighed 330 Gm. The pulmonic ring was 8 cm. in circumference. The cusps were normally thin. The cavity of the right ventricle from the apex to the pulmonic ring was about 9 cm. long. The trabeculae carneae of the right ventricle were much larger and firmer than those of the left, and averaged from 2 to 4 mm. in diameter, whereas those in the left ventricle were slender. The wall of the pulmonary conus in front was 7 mm. thick. The front wall of the right ventricle, exclusive of the trabeculae carneae, was about 6 mm. thick; at the apex from 2.5 to 3 mm. The tricuspid ring was 13 cm. in circumference. A foramen ovale was not present. Surfaces made by sectioning the front wall of the right ventricle were composed of large regions of brown moist myocardium. In other places the myocardium was brown and dry.

Orange-yellow, irregular, soft, slightly elevated regions, similar to those in the main branches, were present in the lining of the branches of the third and fourth divisions of the pulmonary arteries. The lungs were crepitant throughout. At the apex of the left lung there was a thin scar in the pleura. The lung tissue was inelastic, but the lungs partly collapsed after they were opened. The course of some of the second and third divisions of the pulmonary artery was slightly tortuous. The circumference of the main branch to the left lung was 2.5 cm., of the first divisions 1.5 cm. The total pulmonary arterial vascular bed did not appear to be greater than usual. The pulmonary veins were unchanged.

The mitral ring was 10 cm. in circumference, the aortic 6.5. The mouths of the coronary arteries were patent. The lining of the left circumflex branch was light gray and smooth. The right coronary artery was almost twice as large as the left, its lining everywhere smooth.

The spleen weighed 255 Gm. The connective tissue of the gastrohepatic ligament was light yellowish green and markedly edematous. The biliary lymph glands were gray-yellow, and very wet, and some were about 2.5 cm. long. The lining of the portal vein was smooth and gray-white, that of the hepatic artery intact. The lining of the common, cystic and hepatic bile ducts and of the gallbladder was normally trabeculated and light brown. The gallbladder wall was from three to four times normal thickness. The lower fifth of the front of the liver was firm from gray-white stellate scars in the capsule. Surfaces made by sectioning the liver were moderately bloody, moist and mottled light brown and

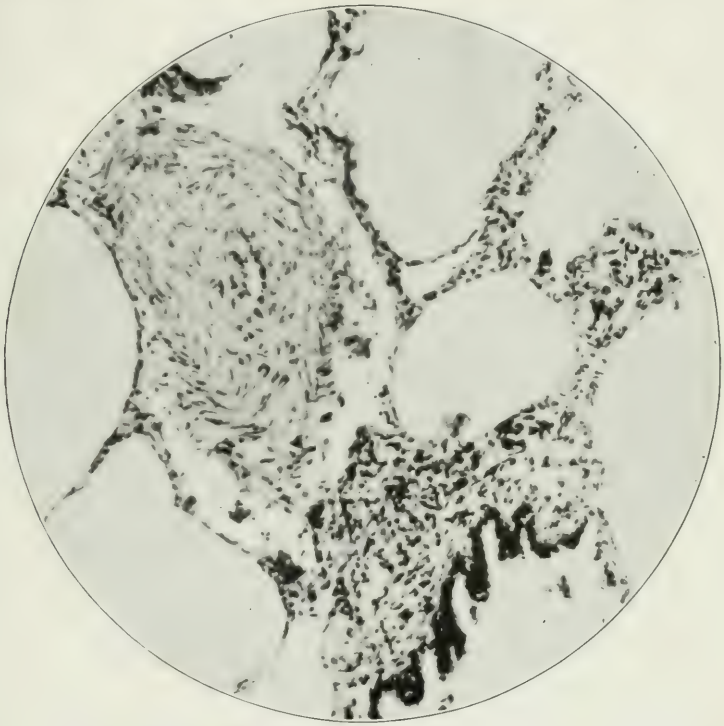


Fig. 1.—The marked diminution of the lumens of the smaller pulmonary arteries, due to extensive proliferation of fibrous tissue in the intimal and subintimal layers, is characteristically illustrated. Magnification × 140.

brown purple to almost black in the upper part of the right lobe. The lobules were coarse. There was a marked increase in fibrous tissue in the periportal spaces. The liver weighed 1,040 Gm. The scars in the capsule did not extend into the liver.

In the stomach there was about 100 cc. of light green semisolid material mixed with mucus. The lining was generally pink and normally rugate. The pancreas was light purple on surfaces formed by cutting. Its duct was normally translucent. There were a few transverse wrinkles in the lining of the splenic artery. The lining of the lower half of the rectum was light gray.

Histology. In the microscopic preparations of the dorsal portion of the upper lobe of the right lung, stained with hematoxylin and eosin, most of the alveoli were empty. The alveolar walls were thin in a few places, but in others about normal thickness; the capillaries were filled with erythrocytes. In the arteries from 0.25 to 0.5 mm. in diameter, the intimal and subintimal coats were thickened by fibrous connective tissue so that they were from two to three times as thick as the middle muscular coat, diminishing the lumens, most of which were eccentric, to about one sixth or one seventh of the greatest diameter of the

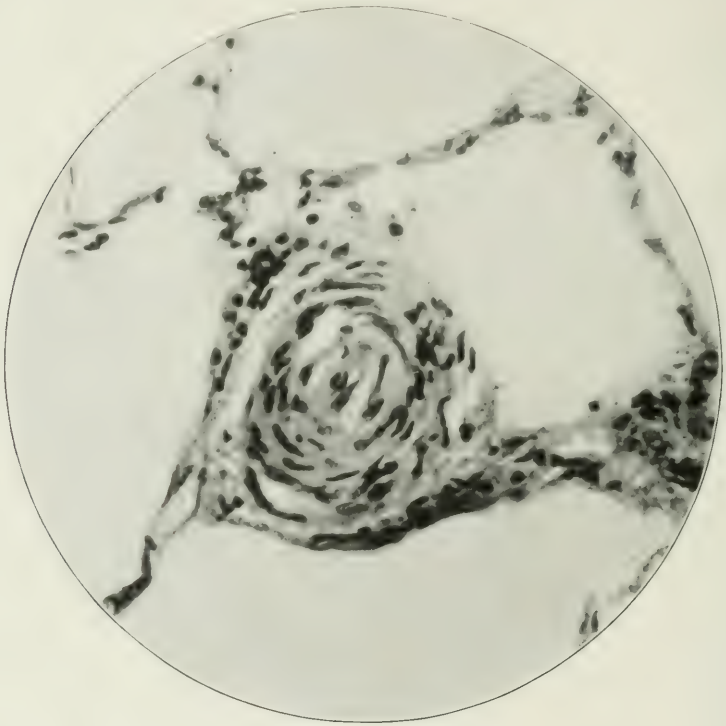


Fig. 2.—The striking microscopic alteration in primary sclerosis of the pulmonary artery and its branches is represented by the changes of this arteriole; everywhere throughout the lungs, there are arterioles with lumens correspondingly reduced, and occasionally some are found which are obliterated by thrombi. Magnification × 350.

vessel. This fibrous tissue in most places was slightly vacuolated. The media in most of the arteries was about the same thickness throughout. The adventitia was composed of loose fibrous tissue. The lumens of the arterioles (precapillary arterioles) were considerably more diminished than those of the larger arteries (figs. 1 and 2). Round cell infiltrations were not observed in the walls of the arteries and perivascular tissues. In a few of the arterioles, organized thrombi completely or partially filled the lumens. Moderate coal pigmentation of

the peribronchial tissues was present. The lumens of most bronchi were empty, and the mucous membrane was normally thin. Some of the alveoli in the dorsalmost parts of the lung were collapsed.

In sections stained with Weigert's elastic tissue stain, the amount of elastic tissue varied considerably. In the larger branches where the lumen was eccentric the thin portion of the intimal and subintimal layers was rich in elastic fibers, whereas in the thicker portions there were only thin strands. In the precapillary arterioles elastic tissue was sparse; in fact, there was none in many such vessels internal to the media. In the pulmonary veins important changes had not occured.

In the dorsal and ventral portions of each lobe and the middle of each lobe, the changes were as extensive as in the right upper lobe, the only difference being that dorsally there was slight atelectasis, and in the ventral portion distention of the alveoli.

The yellowish brown elevated regions in the intima of the pulmonary artery were like those in the main portion.

In sections of the lung and pulmonary arteries stained with sudan III, fat was found in the larger branches in the intima, but there was practically none in the precapillary arterioles.

In sections of the liver, the central portions of most lobules were made up of dilated vascular spaces and extensive destruction of hepatic cords was observed. Noteworthy changes had not occurred in the periportal spaces.

In the wall of the right ventricle at the pulmonary conus there was considerable edema of the interstitial tissues. In a few regions near places where the myocardial fibers had almost disappeared, there was a moderate infiltration of plasma cells, a few round cells and polymorphonuclear leukocytes. Striation of most of the muscle cells was indistinct. The brown pigment close to the nuclei was sparse. In the back wall of the right ventricle there were a few regions in the myocardium from one half to one third of the size of a low power field, in which the muscle bundles were thin and separated by fibrous tissue and an abundance of pink granular material. The intima of some of the arterioles was slightly thickened, in some places equaling the media, but nowhere was there diminution of the lumen similar to that in the vessels of the lungs. In this part of the heart there was an abundance of brown pigment in muscle cells near nuclei. In the adventitia of the arterioles and perivascular tissues noteworthy changes had not occurred.

In the thyroid gland most of the alveoli were filled with colloid-like material, a few of them empty and small. The epithelium of most alveoli was in a single layer, but in a few places it was from two to three layers deep.

In the suprarenal glands engorgement of the capillaries was seen, with erythrocytes and slight thickening of the walls of some of the veins, chiefly the adventitia.

In the kidneys most of the glomeruli were intact. The capsules were thin and tufts engorged with red cells. In the larger arteries at the junction of cortex and medulla the intima was slightly thickened with fibrous tissue. The intima of the larger arterioles in the cortex was not changed. About one glomerulus in fifty was completely hyalinized and shrunken. In the medulla there was marked engorgement of the veins.

SUMMARY

Clinically, the illness of this patient corresponded closely with those cases described by Posselt and Eppinger. Cyanosis was present for four years, but evidence of myocardial insufficiency did not become conspicuous until eight months before death. The cyanosis was never as severe as in Ayerza's disease. Hypertrophy of the right ventricle was demonstrated four years before death. Edema of the subcutaneous tissues appeared eight months before death, but shortness of breath was

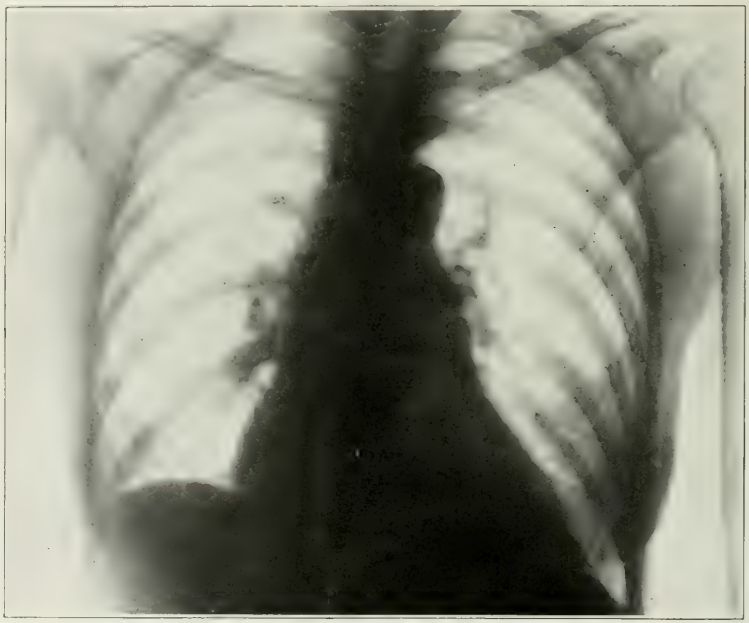


Fig. 3.—Roentgenogram made nine days before death; at this time cyanosis, subcutaneous edema and shortness of breath were pronounced; enlargement of the heart to the right, clear lung fields and bowing in the upper half of the pulmonary and left auricular areas are the outstanding characteristics.

never proportionate to the edema or cyanosis. This illness, as in many of the other studies, was confused with mitral stenosis.

The lung fields during the period of maximum shortness of breath and cyanosis were clear in roentgenograms (fig. 3). The outline of the left auricle indicated that this portion of the heart was not enlarged. These observations are inconsistent with mitral stenosis or other valvular or myocardial diseases of the left side of the heart when the myocardium is obviously inadequate.

The chest was not enlarged, which helped to exclude hypertrophic emphysema of the lungs. The excursion of the lungs posteriorly was about 2 cm., and roentgenograms did not show any evidence of extensive pleural adhesions.

Development of the disease insidiously, following a severe pulmonary infection, when the patient was 32 years old, excluded congenital heart disease.

Posselt described spasmodic severe thoracic pain resembling that of angina pectoris but usually in the right side. Four years before death, thoracic pain was present in our patient somewhat resembling the paroxysms of angina pectoris, occurring during exertion, and she "would have to stop walking." At that time a diagnosis of acute pleuritis was made.

Polycythemia is an unimportant clinical feature of the condition described by the Germans. Two blood counts, in 1922 and 1925, respectively, demonstrated a secondary anemia and leukopenia. During the terminal period the red blood cells numbered 6,080,000, the hemoglobin content was 85 per cent (Dare) and the white blood cells numbered 7,000.

Summary of Morbid Alterations.—The marked diminution of the channels of the pulmonary arterioles (figs. 1 and 2), present in all parts of both lungs, was due to intimal and subintimal proliferation of fibrous tissue in which there were retrogressive changes, without cellular exudate, resembling, therefore, senile arteriosclerosis. Similar alterations were present in the bronchial arterioles, but to only a slight degree. The long continued lessened flow of blood through the lungs had resulted in atrophy of the walls and diminution in the cavities of the left auricle and ventricle; in the latter the trabeculae carneae were small.

The caliber, walls and mouths of the pulmonary veins had not changed anywhere. Some authors have described stenosis of the pulmonary veins as the alteration which causes hypertrophy of the right ventricle and sclerosis of the pulmonary artery. By others it is believed that the diminution of the circumference of the larger pulmonary veins is due to atrophy of disuse.

The only thoracic deformity was a slight scoliosis, the deviation from the midline to either side being only a few centimeters.

The fibrous adhesions in the pleural cavities were less extensive than those commonly found in bodies in which cardiac alterations are not observed. It is estimated that only one fifth of the pleural cavities was obliterated by fibrous adhesions.

Hypertrophic emphysema, or genuine emphysema of Kaufmann, is the only form of pulmonary emphysema that is a primary cause for

hypertrophy of the right ventricle. Compensatory and senile emphysema are associated with a large right heart only when other conditions, such as bronchiectasis and bronchial asthma, are present. In medical literature, the term emphysema of the lungs is used frequently without the type being qualified. It is well known to pathologic anatomists that hypertrophic emphysema is an anatomic entity and the one form of emphysema that is characteristically associated with hypertrophy of the right ventricle and, during life, with cyanosis and cardiac insufficiency. The lungs in our case were still somewhat elastic, collapsing considerably after removal from the body. Coal pigmentation was marked in all parts, another indication that most of the alveolar walls were still intact. The lungs were practically bloodless and the right weighed 215 Gm., the left 175 Gm., which is additional evidence against hypertrophic emphysema, in which disease the lungs usually weight from 800 to 1,000 Gm., each. Posselt and Eppinger called attention to the paleness and bloodlessness of the lungs in primary sclerosis of the pulmonary artery, which were two characteristics of the lungs of this body.

The wall of the right ventricle was hypertrophied, especially the pulmonary conus and the trabeculae carneae. The circumference of the pulmonary ring and artery was not increased. The circumference of the main portion of the right coronary artery was twice as great as that of the left. The scars of the myocardium of the right ventricle were most numerous in the front wall. Some resembled healed Aschoff bodies.

The changes in the aorta and its main branches were not more than are frequently found in early adult life. Sclerosis was present in the small arteries of the kidneys, myocardium, spleen and other organs, but only in a slight degree.

The spleen is enlarged in Ayerza's disease. The spleen in this patient was never palpated during life, and the slight increase in weight (spleen 225 Gm.) is explained by passive hyperemia.

A large part of the pericardial sac was obliterated by fibrous adhesions, but the sac was not adherent to the chest wall or to the lungs, except by a few fibrous adhesions. We do not believe that this alteration accounts for much of the cardiac enlargement, because when enlargement of the heart is due to obliteration of the pericardial sac the left ventricle is preponderately enlarged, and the degree of change present in our case is frequently found at autopsies when there is not any demonstrable cardiac enlargement.[15]

15. Fatty changes and sclerosis of the pulmonary artery are frequently found at necropsies. They are most extensive when there is obstruction to the pul-

(Footnote continued on following page)

Etiology.—A specific etiologic factor was not demonstrated by our examination. Gross or microscopic changes characteristic of syphilis were not found, and unfortunately a Wassermann test was not performed during life.

The patient suffered from two severe infectious diseases, rheumatic fever at 8 years and influenza at 32. The obliterative pericarditis and fibrous myocarditis may be attributed to the former. The patient stated emphatically that the last illness came on insidiously after influenza and pneumonia. This association is important because Le Count [16] demonstrated that one of the characteristic anatomic changes of influenza during the epidemic of 1917-1919, was necrosis of the pulmonary capillaries. Others [17] have emphasized the relation of arteriosclerosis to infectious diseases.

CONCLUSIONS

The clinical and anatomic characteristics of primary sclerosis of the pulmonary artery are described, and a report is made of one case that the authors believe is typical of this disease.

Even though primary sclerosis of the pulmonary arteries is a rare disease, its anatomic and clinical manifestations are so characteristic that it should be recognized during life, if it is borne in mind when search is being made for the cause of enlargement of the right side of the heart.

Ayerza's disease has not been defined clinically and anatomically as characteristically as primary sclerosis of the pulmonary arteries. Some of the cases reported as Ayerza's disease resemble the latter disease, but others are obscured by extensive alterations in the lungs and by associated cardiac disease.

October 11, 1926.

---

monary circulation. This form of sclerosis is named secondary sclerosis of the pulmonary artery by Posselt. Following the increased number of reports of the two conditions described here, cases were reported of chronic pulmonary and cardiac diseases associated with sclerosis of the pulmonary artery (presumably secondary to obstruction of the pulmonary circulation), and the sclerosis was made the cause for many of the cardiac symptoms during life. The German authors have, therefore, emphasized the importance of excluding from the group of "primary sclerosis of the pulmonary artery," all cases in which pulmonary, cardiac or thoracic diseases are present which may obstruct the pulmonary circulation.

16. Le Count, E. R.: Disseminated Necrosis of the Pulmonary Capillaries in Influenzal Pneumonia, J. A. M. A. **72**:1519-1520 (May 24) 1919; Pathologic Anatomy of Influenzal Bronchopneumonia, ibid. **72**:650-652 (March 1) 1919.

17. Posselt (footnote 3). Jores, L.: Arterien, Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2.

LEUKOCYTES AND LACTATION

V. E. EMMEL

This is a report of studies by V. E. Emmel, H. L. Weatherford and M. H. Streicher on the relation of leukocytes to lactation. Contrary to prevalent statements that no definite leukocyte reaction occurs in relation to the activities of the mammary gland, the results obtained demonstrate a pronounced leukopenia during active nursing in the albino rat. The results of a comparative study with reference to numerical neutrophilic and lymphocytic changes, lymphocytic azurophil granulation, erythrocytic reticulation, and polychromasia indicate fundamental differences between this leukopenia and that of inanition.

A quantitative study of leukocytic elements within the mammary tissues demonstrates an increased passage of lymphoid cells into the mammary alveoli and of neutrophils into the ducts in correlation with the circulatory leukopenia.

These correlated changes within the circulation and the mammary gland emphasize the rôle of leukocytes in colostrum and milk formation. Recent investigations demonstrating the fundamental importance of colostrum, on the one hand (Theobald Smith), and leukocytic secretions in growth (Carrel), on the other, together with evidence indicative of bactericidal properties in milk (Hanssen), lend increased significance to this participation of leukocytes in mammary activity.

(The complete article is published in the *American Journal of Anatomy*. **38**:1, 1926.)

DISCUSSION

D. J. Davis: Is there a constant leukocyte content of the milk of rats?

V. E. Emmel: Apparently not.

October 11, 1926.

CARCINOID OF THE APPENDIX VERMIFORMIS

(BY TITLE)

R. S. LEADINGHAM

From the Department of Pathology, Emory University

Carcinoid of the appendix has, until recently, been considered rare. Because of the increasing practice of examining histologically tissues removed by operation, this tumor is being found more frequently.

It is relatively benign, occurs as a small, circumscribed, firm tumor within the lumen of the appendix or as an infiltrating growth along the entire length. It usually is confined to the mucosa and submucosa, seldom invades the muscularis and rarely penetrates the serosa. Its presence may be determined only by microscopic examination.

The nature of the tumor has occasioned considerable discussion. Some claim that the small, pale, spheroid cells characterizing most of the growths

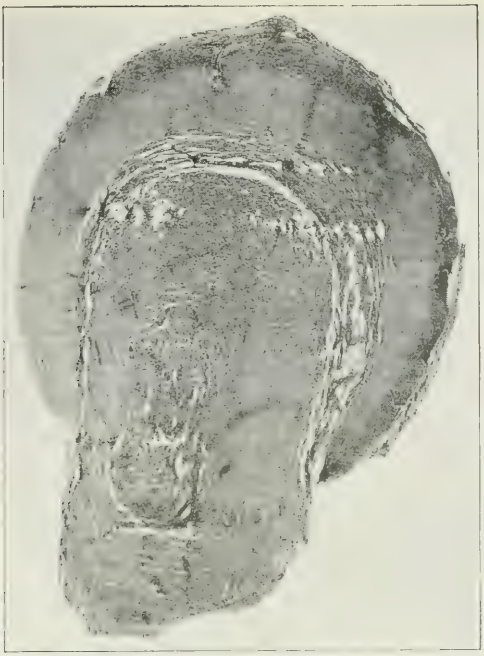


Fig. 1.—Carcinoid of the appendix.

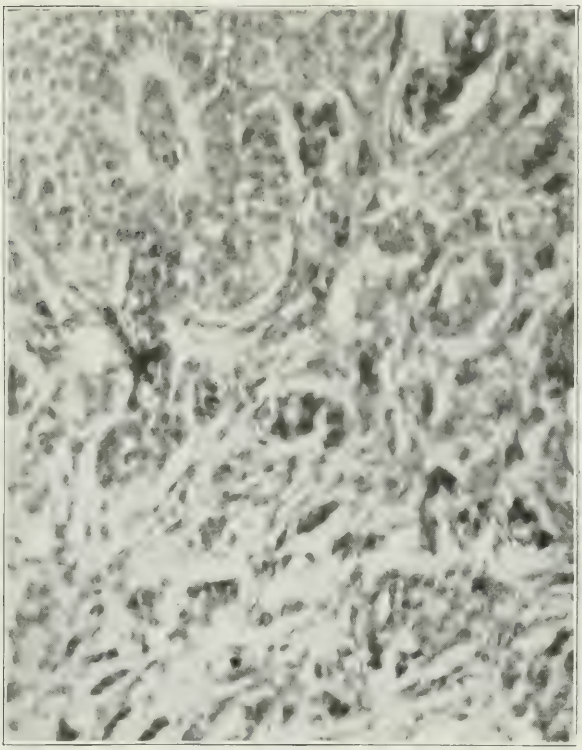


Fig. 2.—Carcinoid of the appendix.

suggest endothelial rather than epithelial origin. However, the presence of columnar cells and the alveolar arrangement have led many to regard them as slow growing carcinomas.

The tumor here reported was removed incidentally during an operation for removal of an ovarian cyst, and was overlooked in the operating room and laboratory until microscopic sections were examined.

The tumor was 7 mm. long, and 3 mm. wide. It obliterated the lumen, and extended 3 mm. beyond the wall.

There were plaques of small, pale, spherical cells, and ill-defined acini, lined by cells of the columnar type. They were separated by a dense connective tissue stroma, in which focally were a few round cells.

The tumor was obtained from the surgical service of Dr. W. S. Goldsmith.

October 11, 1926.

THE NORMAL BACTERICIDAL MECHANISM OF THE GASTRO-INTESTINAL TRACT

PRESIDENTIAL ADDRESS

LLOYD ARNOLD

Some of the results of this study can be summarized briefly as follows:

By operative procedures certain segments of the small intestine are fixed to the anterior abdominal wall in such a way that material can be obtained for study.

The normal reaction of the content of the duodenum and upper part of the jejunum is slightly acid (p_H from 5.2 to 6.5). When this reaction is made alkaline, there is a change from the usual obligate bacterial flora to a fecal type. The normal hydrogen-ion concentration of the content of the duodenum and jejunum seems to depend to a great extent on the normal gastric secretion.

Some of the nutritional disturbances have been explained on the basis of this bactericidal property of the upper part of the small intestine. Moro's endogenous infections in infants were given particular attention, and the beneficial results that have followed the ingestion of protein milk, buttermilk, lactic acid milk, hydrochloric acid milk and all such acid buffered foods are regarded as influencing to a great extent the duodenal function of the infant.

Bacteria introduced into the dog's stomach with alkaline buffered milk reach the cecum in large numbers during a relatively long period. When the same bacteria are given by mouth in acid buffered milk, they sometimes reach the cecum, but in small numbers, and during a relatively short period. Bacteria introduced into the stomach in an acid buffered aqueous solution seldom reach the cecum. When suspended in alkaline buffered aqueous solution, the bacteria reach the cecum in almost the same concentration as the original ingested suspension. Perhaps the "auto-disinfecting" mechanism of the upper part of the small intestine is dependent on acid buffered material. This reaction is insured in the healthy animal by the normal gastric secretion. When neutral or alkaline buffered material enters the duodenum, the bactericidal power is lost and the bacterial content of such material reaches the cecum.

As a result of a statistical study of the diarrheal death rate in infants under 5 years of age in New York city, it seems that one of the probable factors in the increased resistance of young infants to diarrhea is the extensive use of acid buffered foods during the last decade, as suggested by Finkelstein and others.

Some evidence has been presented to show that mice are rendered more susceptible to infection by mouth of certain paratyphoid bacteria when fed on a diet that contains a relative large amount of alkaline buffered material. Mice fed on a diet that contained much less alkaline buffered substances have a greater resistance to the same dose of the bacteria.

It seems from these results that the normal bactericidal mechanism of the gastro-intestinal tract plays a major rôle in the susceptibility or resistance (nonspecific) of the host to certain enteric infectious diseases.

November 8, 1926.

MESENTERIC CYST OF THE JEJUNUM

BERNARD PORTIS

From the Nelson Morris Memorial Institute for Medical Research and the Surgical Department of the Michael Reese Hospital, Chicago

Cysts of the mesentery of the small intestine are comparatively rare and still less frequently produce clinical symptoms. The cyst of the jejunum described here caused intestinal obstruction. There were several other congenital abnormalities.

Cystic tumors of the peritoneum may be lymphatic or chylous, enteric or urogenital, or they may be dermoids and teratoids.

The chylous cysts are large, single or multilocular tumors, or numerous small swellings of the mesentery, omentum, intestinal wall or retroperitoneal region. They contain clear fluid, chyle or inspissated fatty material, and often blood. The walls are fibrous tissue with many round cells or lymph follicles and often dilated lymph spaces. Smooth muscle tissue may be present as in enteric cysts, and there may be a lining endothelium. Giant cells may form about the fatty detritus.

The enteric cysts are either single or multiple, large or small, usually along the lower ileum, in the wall of the intestine at the place of a Meckel's diverticulum, in the mesentery or near the navel. When originating within the muscular wall of the intestine they remain attached to the convex side or project into the mesentery. They contain mucilaginous, colorless, yellow or brown fluid. The wall resembles that of the intestine and may contain smooth muscle, mucosa, crypts, lymphoid tissue and a lining of cylindric, cuboidal or stratified epithelium, sometimes papillary.

The urogenital cysts are large, single, multiple or multilocular and involve the mesentery and adjacent organs or extend into the pelvis. They occur chiefly in adult women, and contain brown serous fluid with pseudomucin. The wall is fibrous tissue with a cylindric or cuboidal epithelial lining, and there may be suprarenal cortex or tissue resembling embryonal kidney.

The dermoid cysts are rare.

Report.—A girl, aged 5½ years, entered the Michael Reese Hospital on Aug. 11, 1926, service of Dr. Julius Hess, with abdominal pain of eight weeks'

duration, loss of weight and appetite, and constipation. The abdominal pain, located just below the navel, frequently severe, and cramplike in character, usually occurred after eating and continued for from fifteen minutes to several hours. Loss of appetite, weight and strength followed, constipation was marked and vomiting occurred several times.

The essential changes, physically, concern the distended and resistant abdomen. A cystic tender tumor mass was palpated in the lower right quadrant. Peristalsis was not noted at first, but on the following day some was noted in the upper right quadrant. The von Pirquet and Mantou tuberculin tests gave negative reactions. Among the diagnoses considered were tuberculous peritonitis, Meckel's diverticulitis and atypical appendicitis.

Roentgen-ray examination of the chest and abdomen did not disclose any changes excepting an abnormal fixation of the cecum and ascending colon in the liver region, with an irregularity of the cecum that suggested a tumor.

There was a mild secondary anemia; the leukocytes numbered 11,200, the urine contained acetone but not albumin, and the feces did not contain blood.

The child, when seen again on August 17, had symptoms of intestinal obstruction, and an operation was advised. With local anesthesia a right pararectal incision was made, and a tense cystic tumor mass was found. Ethylene anesthesia was then given because of the tumor size. The incision was enlarged, and the tumor mass, about 10 by 8 by 6 cm., was removed from the abdomen. It lay in the mesentery of the jejunum, the jejunum in front like a taenia coli. The intestine on the cyst was almost collapsed. The bowel was resected proximal and distal to the tumor, and the ends closed and inverted. The tumor was then amputated at its mesenteric attachment, care being taken not to interfere with the blood supply. In removing the tumor, one of the cysts was opened and a yellow gray, odorless fluid escaped. The two ends of the intestine were united by a lateral anastomosis and the mesentery was sutured so as to prevent pocket formation.

The report from the pathologic laboratory revealed the following: In a piece of small intestine, between the folds of the attached mesentery, were four, fluid containing, communicating cysts, from 2 to 4 cm. in diameter. Another large cyst which had been opened was 5 by 4 cm. The wall was about 1 mm. thick. The inner surface was corrugated by branching strands of yellow gray tissue. The cysts were all close to the bowel. The outer surface of the cyst was dark red. The cyst wall was composed of fibrous tissue with small bundles of smooth muscle widely separated. There was no recognizable cellular lining. In the wall were a number of dilated lymphatics. The outer portion of the cyst wall was directly continuous with the connective tissue of the outer surface of the intestine. The pathologic diagnosis was "lymphogenous cyst of the mesentery."

The condition of the patient was improved after the operation. Cereals were given the following day. However, attacks of vomiting appeared, the child growing rapidly worse, and death occurred the third day after the operation.

An abstract of the conditions found at necropsy, which was done by Dr. Norbert Enzer, follows: "The abdomen is rounded and has a recent operative wound about 8 cm. in length in the lower right rectus region.

"The pleural and pericardial cavities, the lungs, and the heart are without noteworthy changes.

"The omentum covers the bowel completely. There is a generalized acute fibrinous peritonitis. Most of the small bowel is distended with gas and dusky red but nowhere necrotic. The lateral anastomosis of the two loops of the jejunum from which the mesenteric cyst has been removed is intact, 30 cm. from the pylorus. The stomach is normal; the pylorus is tightly contracted in rigor mortis. The duodenum and the first part of the jejunum are markedly distended. About 15 cm. from the pylorus the bowel passes posteriorly through an opening in the mesentery into an infraduodenal fossa on the left of the spine, beyond which it proceeds upward for a short distance, then to the right and back again through the same opening in the mesentery. This portion of herniated jejunum is markedly distended and dusky red. The hernial sac is a thin membrane resembling mesentery. The herniated loop of bowel is 10 cm. long. About 6 cm. below the hernia and lying just in front of it is the anastomosis. In this region the bowel is distended and discolored, though less marked until about 20 cm. from the cecum; there a second discolored and slightly cyanotic loop of bowel is caught in the same hernial ring."

November 8, 1926.

RIEDEL'S STRUMA OF THE THYROID

O. T. SCHULTZ

Since Riedel in 1896 described a fibrous tissue replacement of the thyroid gland, some forty-five instances of this relatively rare thyroid disease have been reported. Clinically, the thyroid is moderately enlarged, hard and fixed to the surrounding tissues, changes which usually have led to the preoperative diagnosis of malignancy. The surface may be smooth or slightly nodular. The capsule is thickened, and the thyroid tissue is pale, firm and with little colloid.

Among 305 thyroid glands surgically removed at the Michael Reese Hospital since 1917, Riedel's struma was observed three times, two being received in the pathologic laboratory within one month of each other during the present year, and one during the latter part of last year. The three were from women, of the ages 26 and 46 years, respectively. In all, pulse, temperature and respiration were normal. None had exophthalmos, although in two the clinical diagnosis was toxic goiter; in the third, carcinoma. The basal metabolic rate was minus 5 per cent in the first, plus 29 to 34 per cent in the second with repeated tests, and minus 20 per cent in the patient supposed to have carcinoma. In all, the thyroid gland was slightly enlarged, the increase having appeared gradually within from two to six months.

In the youngest of the three patients, whose basal metabolic rate was minus 5 per cent, the thyroid had not been completely transformed into the hard, ligneous tissue present in the other two thyroid glands. In the latter, the follicles were compressed by a large amount of moderately cellular, interfollicular connective tissue, and richly infiltrated by lymphocytes and plasma cells. The follicular epithelium is high and frequently surrounds a small amount of deeply stained inspissated colloid. In many follicles both colloid and lumen have disappeared, the epithelium forming a multinucleated syncytial mass. In a few

follicles less compressed by the ingrowth of connective tissue, the epithelium is low and the lumen filled with deeply stained colloid.

The clinical recognition of the nature of the condition is important, since the usual diagnosis of malignant growth leads to an unnecessary operation, sometimes followed by immediate mortality or by laryngeal paralysis, the latter accident having occurred in this series in the case diagnosed clinically as carcinoma.

The change apparently is a nonspecific granulomatous inflammation, in which thyroid hyperplasia and inflammation of the upper respiratory tract have no part. In the three cases presented nothing could be found corresponding to the remnants of the postbranchial body described by Louise Meeker, whose presence she suggests may be a factor in the transmission of an inflammatory process from the pharynx to the thyroid.

November 8, 1926.

RHABDOMYOMA OF THE TONGUE *

KAETHE W. DEWEY
CHICAGO

Scarcity of records of a given pathologic condition is not always, but frequently, an index of the rarity of its occurrence. The records of rhabdomyoma of the tongue are extremely scanty; as far as I can ascertain, only seven cases have been reported. The first case is that of Weber,[1] reported in 1854, in which the tongue of a patient, aged 21, was as large as a hand, measuring 5 by 2½ inches. He called the condition "hypertrophic tongue." Microscopic features characteristic of the tumors were observed only in the new growth which developed after the first excision of the part protruding beyond the teeth. The second case, published by Pendl[2] in 1897, was that of a boy, aged 8 weeks; the growth was as large as a pigeon egg. All the other reports of rhabdomyoma of the tongue were made this year: Keynes[3] reported one case; Abrikossoff[4] three cases and Rütz[5] one case of a tumor as large as a plum in a boy, aged 5 months.

---

* From the Department of Oral Pathology, College of Dentistry, and the Department of Pathology, College of Medicine, of the University of Illinois.

1. Weber, C. C.: Anatomische Untersuchungen einer hypertropischen Zunge nebst Bemerkungen über die Neubildung quergestreifter Muskelfasern, Virchows Arch. f. path. Anat. **7**:115, 1854.

2. Pendl, F.: Ueber ein kongenitales Rhabdomyom der Zunge, Ztschr. f. Heilk. **18**:457, 1897.

3. Keynes, G.: Rhabdomyoma of the Tongue, Brit. J. Surg. **13**:570, 1926.

4. Abrikossoff, A.: Ueber Myome, ausgebend von der quergestrieften willkürlichen Muskulatur, Virchows Arch. f. path. Anat. **260**:215, 1926.

5. Rütz, A.: Angeborenes Rhabdomyom der Zunge, Med. Klin. **22**:1072, 1926.

Rhabdomyomas may be divided into three groups. Those of the first group are heterotopous tumors; they occur in tissues and organs which normally have no striped muscle tissue. These growths are found chiefly in the urinogenital tract, but have also occurred in the parotid gland, the lung and elsewhere. They are mixed tumors, as a rule, and are relatively the most frequently occurring rhabdomyomas. The second group is next in frequency of occurrence and comprises tumors of involuntary striped muscle; namely, of the heart. These tumors have been well described. The third group represents the rarest type of rhabdomyoma. These tumors occur in voluntary striped muscle, such as that of the tongue and the lip, and the skeletal musculature.

In his recent report of five cases of rhabdomyoma of voluntary striated muscle, three of which were of the tongue, Abrikossoff states that up to 1918 only eight cases of such tumors had been reported and that he had not found any reports since. If these eight cases are added to those published in 1920, including my own, there are records of only sixteen cases altogether. Since eight of these were observed in the tongue alone, and only eight occurred in other parts of the voluntary musculature of the body, rhabdomyoma of the tongue must be considered as relatively the most frequent of this group of tumors.

While in the two cases of congenital rhabdomyoma and in Weber's case of "hypertrophic tongue" the tumors were proportionately large, in the other cases the growths were small, hard, slightly elevated nodules, located in the dorsum of the tongue, paler than normal muscle tissue and more or less circumscribed. In all cases the tumor was without a capsule and without evidences of malignancy. Inflammatory processes were lacking or slight. All were pure rhabdomyomas.

The microscopic appearance of such tumors is striking. The cells of which the tissue is largely composed bear no resemblance to muscle tissue; at first sight, they appear like xanthoma cells, but unlike them are not filled with fat. They are, on the whole, unusually large cells with a light protoplasm which contains numerous fine granules. These cells correspond to the embryonic myoblasts, and in some tumors no evidences of cross striation were observed; such tumors might be called, as Abrikossoff suggests, myoblastmyoma of voluntary striped muscle, or rhabdomyoma nonstriocellulare. The cells also somewhat resemble polymorphous sarcoma cells, and several writers have suggested that the "sarcomatous elements" in some rhabdomyomas, which have been mentioned in older reports, probably refer to areas within the muscle tumor occupied by myoblastic elements. The embryonic nature of the cellular elements of rhabdomyomas also accounts for the fact that rhabdomyomas appear lighter than the surrounding normal muscle tissue,

for embryonic muscle tissue also is lighter than adult muscle. The characteristic histologic features observed in rhabdomyoma of the tongue are the same found in rhabdomyoma of voluntary striped muscle in other parts of the body. Cross striation of tumor cells and cell cylinders have been observed in some tumors; in other cases it was entirely lacking. Abrikossoff found cross striation in two but not in the other of his cases of tumor of the tongue; in a rhabdomyoma of the lip he observed, to a limited extent, an arrangement of the cell granules which resembled the beginning of cross striation. In Keynes' case of rhabdomyoma of the tongue, cross striation was entirely lacking.

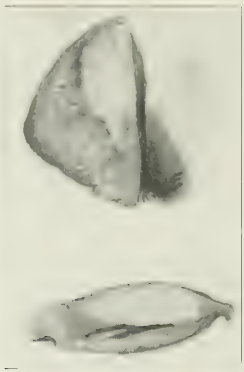


Fig. 1.—The tumor is well circumscribed on the mucosal and the cut surfaces, but is without a capsule. Natural size.

REPORT OF CASE

History.—In the case of a woman, aged 42, a tumor, located on the anterior part of the tongue to the left of the median line, was removed in December, 1925. It appeared as a hard, grayish, slightly elevated mass measuring 1.5 cm. in diameter. The mucosa over the tumor was not ulcerated. Slight itching or tickling, but no pain was felt. There were no palpable cervical lymph glands, and on general examination nothing abnormal was found. The swelling had been noticed first two years before, as a small elevation. There was some treatment, with no results; the growth gradually increased to the size observed at the time of the operation. The clinical diagnosis was carcinoma of the tongue (?). A *V*-shaped excision was made. The wound healed entirely, and at present, eleven months after the operation, there is no indication of a recurrence. A hurried microscopic examination of a frozen section of the tumor led to the diagnosis of fibropseudodoxanthoma of the tongue. I received the specimen from I. Pilot.

The slightly elevated tumor mass was well demarcated on the outer mucosal surface as well as on the cut surface, and it measured 16 by 14 by 6 mm. It appeared denser and paler than the surrounding tissue; the papillae over the

growth were slightly flattened. In a region some distance below the tumor mass there was a relatively extensive hemorrhage in the muscle tissue which as the microscopic examination showed was not incident to the operation.

Since the tissue had been fixed in formalin examination for glycogen was not possible. A number of different stains were made: hematoxylin-eosin, phosphotungstic acid hematoxylin, van Gieson's Mallory's anilin orange blue, Heidenhain's iron hematoxylin, Weigert's for elastic fibers with Hart's modification, and Weigert's for myelin sheaths. Sudan III and Nile blue stains and

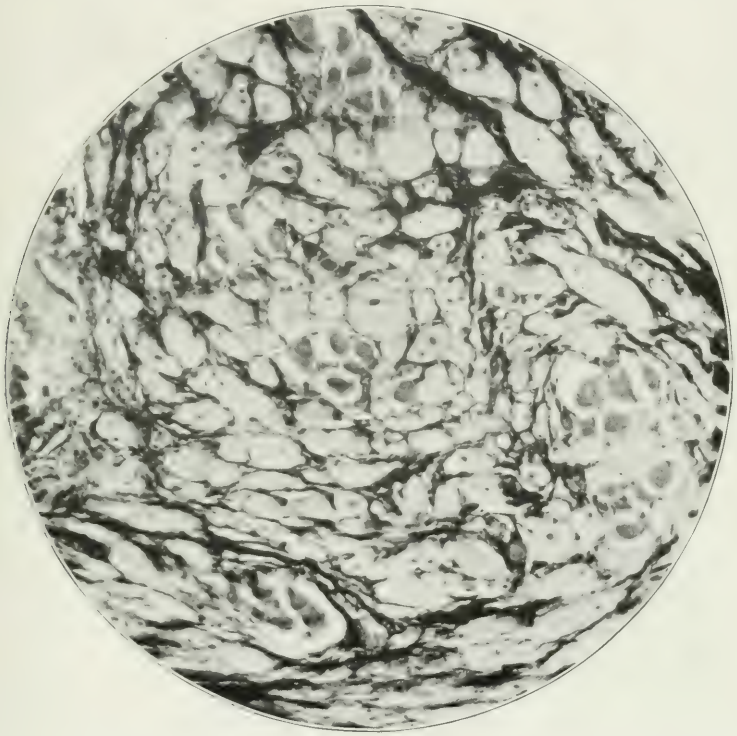


Fig. 2.—The roundish and spindle shaped light cells are distinct and separated by darkly staining, fine and thick collagenous fibers; groups of young muscle fibers intermingle with the cells; each fiber is surrounded by a space. Van Gieson's stain. Magnification 140.

Ciaccio's Lorrain Smith's and Fischler's methods were employed for the demonstration of fat and lipoid substances. Some of these stains require fixation in chrome salts; in those cases, secondary fixation of paraffin sections in Zenker's fluid for twenty-four hours secured entirely satisfactory staining results.

Microscopic Examination.—In all sections the tumor tissue was well defined from the neighboring tissue by the greater density of texture and the much slighter staining quality. The most striking histologic feature was the appear-

ance of the cells of which the tumor tissue was largely composed, which at first sight resembled xanthoma cells. They were large, roundish cells with a darkly staining nucleus located in the center, and a light protoplasm which contained numerous fine granules. Although they varied considerably in size the average diameter was greater than that of the muscle fibers surrounding the tumor mass. The average size of the cells was 38 microns; the largest measured 54 microns, the smallest 21 microns. The preexisting muscle fibers of the tissue at the bottom of the tumor showed considerable inequality of thickness; some were swollen; the largest were 42, the smallest 17 microns

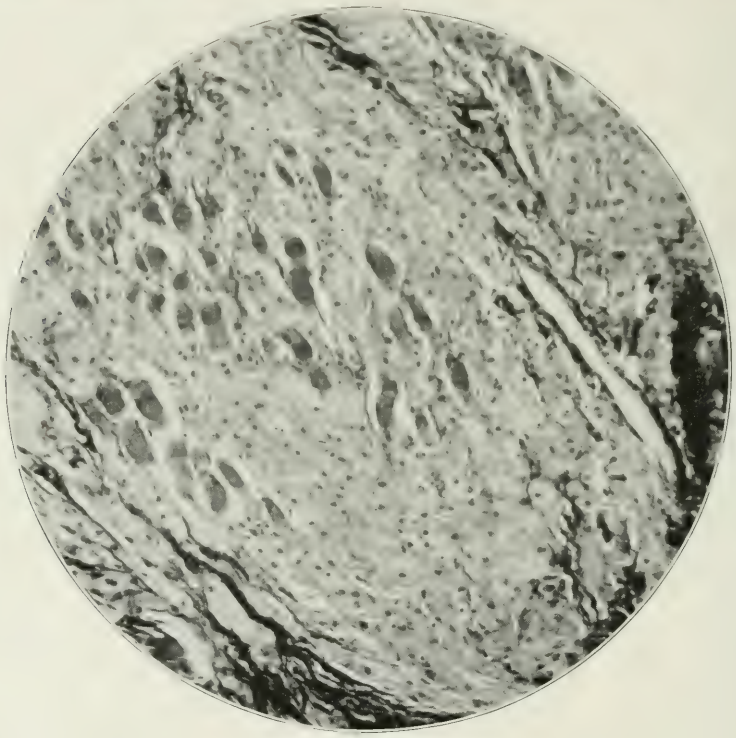


Fig. 3.—Another field in the section shown in figure 2 in which the cells are more or less completely fused and form a syncytium, while the young muscle fibers have definite outlines and are surrounded by a space. Magnification 140.

in diameter; the average thickness was 26 microns. The muscle fibers alongside the tumor tissue showed atrophy; their thickness ranged between 8 and 21, with an average of 14, microns.

The roundish cells, which were often polyhedral from mutual compression, extended to the epithelial border and into the papillae, and they infiltrated the adjacent muscle tissue to a slight extent. Areas in which large and smaller polyhedral cells were arranged mosaic-like alternated with areas in which the cells were joined lengthwise and formed cylinders. These were more or less

parallel one to another, and were sometimes long and even and sometimes shorter, curved and interweaving, so that they appeared with tapered ends. In some of these cell cylinders the individual cell outlines were retained, in others they were more or less obscured or completely lost. The individual cells generally contained one nucleus; rarely there were two and exceptionally four nuclei were seen together. The nuclei were as variable in size and shape as the cells. The average nucleus was roundish or oval, not large in proportion to the size of the cell and rich in chromatin, and it contained one or two large darkly staining nucleoli. Larger nuclei sometimes showed more than two nucleoli — even six could be counted; also relatively large nuclei were seen. While the larger nuclei were roundish or oval, the smaller ones were angular, cuboidal or with other irregular forms. Not rarely more or less homogeneous darkly stained small masses were seen in the cells, and particularly in the cell cylinder; they were remnants of nuclei. Throughout the entire tissue, and in all stains, the cell body with its granular protoplasm appeared light. In some cells the granules were close together and uniformly filled the entire cell body; in others there was the appearance of some grouping of the granules, sometimes only vague, sometimes fairly distinct. This grouping suggested an arrangement of the granules in stripes, but in no instance could it be called definite. Another grouping of cell elements, however, was sometimes observed which was definite, and in appearance absolutely identical with Cohnheim's fields. Occasionally the entire transverse surface of a cell was divided into such fields; more often only a few were seen in one cell. They were often unequal in size, and here and there a giant field of Cohnheim was seen. Such fields were also observed occasionally on the longitudinal aspect of a cell cylinder. In this position they seemed incongruous; Cohnheim's fields indicate an arrangement of granules and a formation of fibrils in a definite direction; in adult muscle fibers they represent the cross-sections of longitudinal bundles of fibrils within the fibers. Cell cylinders are the forerunners of muscle fibers; they are formed by the union—often pell mell—of individual cells, and it was assumed that in some of the latter a grouping of granules and fibrils into bundles had already taken place, while orientation of the bundles within the cell cylinders had not yet occurred.

The cells and cell cylinders had definite outlines; but there were areas in which the cells were fused and had lost their membranes, i. e., syncytium formation had taken place. The syncytium corresponded to the plasmatic syncytium observed in embryonic life as a phase in myogenesis. The presence of delicate cell membranes, except in the syncytial masses, and of intercellular fibrils and fine and coarse fibers was well brought out by van Gieson's stain and Mallory's stain for collagenous fibers. As the cells of this tumor corresponded to the myoblasts, the intercellular collagenous fibrils and fibers represented the perimysium, including the sarcolemma. The amount of this intercellular connective tissue varied greatly; in some areas it consisted only of fine fibrils, in others it was considerable and occurred even in broad bundles which were not unlike narrow muscle fibers. The collagenous fibers were accompanied by elastic fibers. In sections stained by Hart's modification of Weigert's stain for elastin, it was found that elastic fibers were entirely absent in the syncytium and in areas in which the cells were closely packed and separated only by their cell membranes. With an increase of the intercellular collagenous tissue elastic fibers appeared. There were only a few in the cellular tissue, but they became more apparent

about the cell cylinders in the neighborhood of muscle fibers about which they were always in evidence, and were present in abundance in the subepithelial tissue and the papillae where the connective tissue was more abundant. There were fewer elastic fibers about degenrated muscle fibers in the tissue outside the tumor mass.

Scattered throughout the cellular tumor tissue adult muscle fibers were found running longitudinally and transversely; they were always in groups.

Fig. 4.—Between the young muscle fibers is a cell cylinder with contorted outlines, composed of cells, the membranes of which have disappeared in the lower part and are partially retained in the upper part; the nuclei are large and dark, and here and there a grouping of the cell granules in stripes can be seen; the two outer muscle fibers show longitudinal fibrillation and a cross striation which is fine and close, and often discontinuous; the transverse stripes of the central muscle fiber are thicker, farther apart and continuous; faint suggestion of longitudinal and cross striation in cells to the right and plainly visible Cohnheim's fields in cells to the left. Mallory's stain for collagen. Magnification 380.

Some of the longitudinal fibers which were very long extended almost throughout the entire width of the tumor in the sections. There were evidences that these muscle fibers were largely, if not all, newly formed and not remnants

of preexisting muscle fibers which were destroyed by the growth of the tumor. Degenerative changes were not evident in these muscle fibers, except slight ones here and there at the periphery, which were of the same type as those present in the muscle tissue outside the tumor. Here the changes were quite marked and, apparently, were not brought about by the growing tumor, but arose, perhaps, in part from disturbances due to trauma. At some distance from the inferior border of one half of the tumor there was an extensive

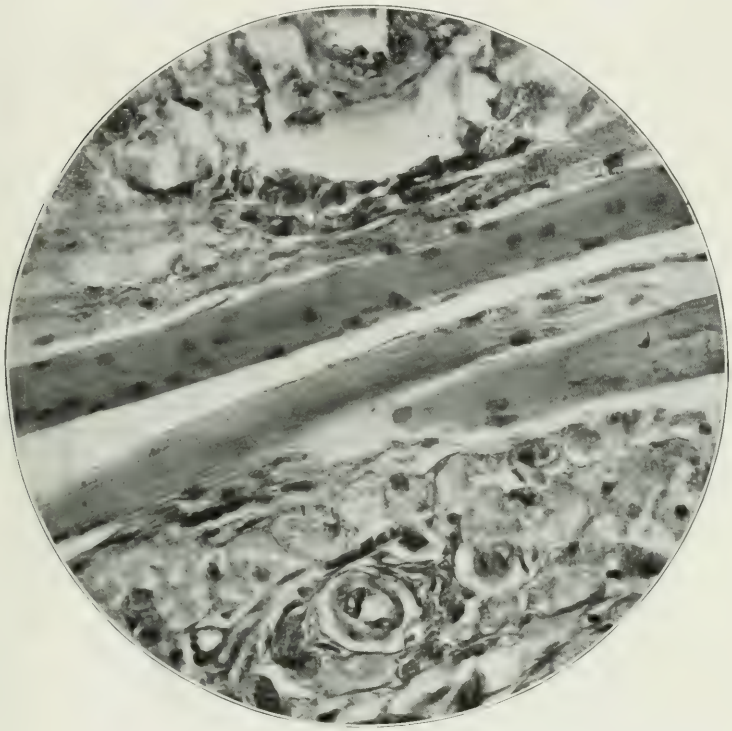


Fig. 5.—Of the three young muscle fibers in this field the upper and the lower one contain numerous large round nuclei scattered throughout the interior of the fibers; their development through fusion of many cells is obvious where shadows of cell outlines are still discernible; there is only longitudinal fibrillation in these two muscle fibers, while the more adult central muscle fiber shows distinct cross striation; there is a fairly distinct grouping of the cell granules in a longitudinal direction in the slender cell cylinder above and along the upper muscle fiber. Van Gieson's stain. Magnification 335.

hemorrhage, which was not of recent date, and here the muscle fibers had undergone most marked lytic alterations. Other changes of the muscle tissue around the tumor were well demonstrated by phosphotungstic acid hematoxylin, Mallory's anilin orange blue and Heidenhain's iron hematoxylin stains. With Mallory's stain the color changes of the adult muscle fibers ranged from vivid

scarlet red to purplish red, lavender and purple. With Heidenhain's iron hematoxylin stain those fibers which were scarlet red with Mallory's stain were deep black. Such fibers appeared as markedly swollen, homogeneous, brittle masses in which longitudinal and cross striation had largely or totally disappeared; transversely cut fibers of this kind showed clefts. In fibers showing other color reaction the original structure was also more or less obliterated. Longitudinal striation was more resistant than cross striation. All these changes were absent in the muscle fibers which occurred in the tumor tissue

Fig. 6.—Tumor cells, very irregular in size and shape, occupy the papillae and are actually in contact with the epithelium; a suggestion of cross striation may be seen in some cells; the outer epithelial surface is flat and without any cornification. Van Gieson's stain. Magnification 140.

as a result of differentiation of the cellular elements. The process was best observed about the longitudinal muscle fibers, between and around which cell cylinders were present. Some of the cylinders already showed complete fusion of the individual cells and were as straight and evenly contoured as adult muscle fibers. In others the cell membranes were still partially or totally retained; such cylinders were twisted and unequal in width, and showed constrictions. It is to be assumed that the cells mixing with, and surrounding,

transversely cut young muscle fibers were the transverse sections of cell cylinders running parallel to those muscle fibers. A grouping of cell granules that was suggestive of an initial cross striation generally was found in cell cylinders near the newly formed muscle fibers. The fact that very distinct Cohnheim's fields were seen in the cells here and there, also indicated that a systematic arrangement of elements within the cells had already taken place, but that the greater affinity for the stain was still lacking. Occasionally, however, in the vicinity of adult muscle fibers, cells were observed which were

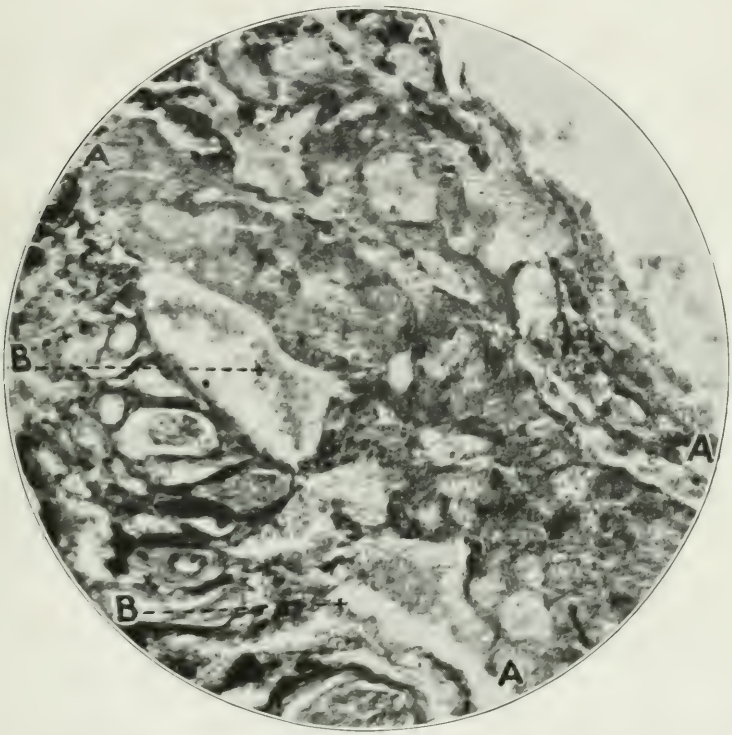


Fig. 7.—From a tongue involved in marked granulomatous infiltration with extensive destruction of the muscle tissue; in the area (*a*) to the right the degenerated muscle fibers are broken down and appear as irregular cells in which traces of longitudinal and cross striation can be seen here and there; the chief difference between these cells and those in the tumor tissue is the almost complete absence of nuclei; (*b*) blood occupying all available spaces to the left. Mallory's stain for collagen. Magnification 250.

slightly darker than the other cells, which also exhibited initial stages of cross striation, while the nuclei were less distinct. The cell cylinders next to adult fibers became invested with some connective tissue like those fibers. Spaces which were always present about adult muscle fibers were sometimes also seen

about cell cylinders adjacent to the muscle fibers. Such spaces were totally absent in the strictly cellular tissue.

An interesting feature of the development muscle fibers was the change of the position of the nuclei. In the cells and the cell cylinders the nuclei were rather large, roundish and axial; in the adult muscle fibers they were narrower, spindle-shaped, darker and superficial. There were also transitional fibers which already had the darker stain of young muscle fibers, but the nuclei were still roundish and scattered in the central portion of the fiber, and structurally were less distinct than the nuclei in the cells and the cell cylinders; this was

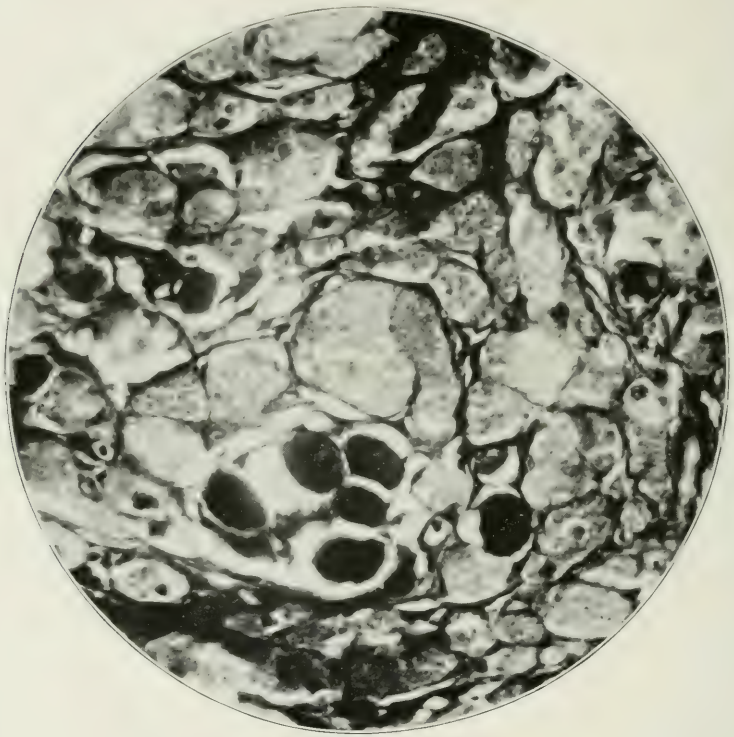


Fig. 8.—From the tumor tissue. Mallory's stain for collagen. Magnification 335.

due in part to the fact that they were dimmed by the darker stain of the muscle fiber. Such young fibers were sometimes as evenly contoured and straight as the more adult fibers; but the union from many irregularly shaped cells was still discernible, for shadows of cell membranes within the fibers could be seen. Apparently some nuclei perished in the course of the formation of muscle fibers, for nuclear remnants were especially numerous in the cell cylinders near muscle fibers. Cross striation was less distinct in fibers with axial nuclei than in those with peripheral nuclei.

Muscle fibers obviously did not develop from one cell, nor grow by increase in length of this one cell, but they developed through fusion of many cells.

In the cell cylinders resulting from this fusion at first the nuclei were placed axially, and gradually they came to lie at the periphery. Also this process corresponded to a phase in embryonic myogenesis.

The formation of muscle fibers began at a certain distance from the epithelium. There was no indication of such processes in the tumor tissue occupying papillae and the subepithelial region. The cellular tissue in this location generally appeared lighter than the rest of the tissue.

The subepithelial tumor tissue, on the other hand, was the one in which a reaction, however slight, to the lipoid stains was observed. Abrikossoff reported of his cases that staining with scharlach R was negative. I observed a slight reaction with Sudan III while sections stained with Nile blue were negative. With Ciaccio's method which demonstrates complex mixtures of lipoid substances, in particular kephaline, a somewhat more definite reaction was obtained than with Sudan III; with this staining, the tumor cells in the subepithelial and papillary regions appeared filled with faintly orange colored granules. Whether this reaction was more extensive than these sections indicate could not be ascertained, for the piece of tissue prepared by Ciaccio's method contained only a small area of tumor tissue. No lipoid substances demonstrable by this method were observed in the muscle tissue outside the tumor tissue. As to Fischler's method which demonstrates fatty acids and soaps, only thick sections revealed a somewhat characteristic reaction; namely, a slaty bluish coloration of the granules in cells and cell cylinders, chiefly in the subepithelial region. Some of the muscle fibers outside the tumor tissue, however, showed a characteristic reaction to Fischler's stain, i. e., a black coloration. This was observed in the homogeneous, swollen muscle fibers staining scarlet red with Mallory's stain and black with Heidenhain's iron hematoxylin. The same reaction was observed in parts of the surface epithelium, which was cornified. From the reactions to Ciaccio's and Fischler's staining methods it might be concluded that the lipoid substances present in small amounts in some parts of the tumor tissue are chiefly of the nature of cholesterol compounds, kephaline mixtures and fatty acids. Their presence was probably an expression of degenerative changes that had taken place in these parts.

The vascular supply of the tumor tissue was limited and the infiltrative processes were slight.

COMMENT

The tumor in this case, while largely composed of atypical cells, nevertheless revealed features which clearly showed the myogenic nature of the tissue. The elements and phases of normal embryonic muscle development were also observed, although in a more atypical manner, which is practically characteristic of tumors in general. There were deficiencies in differentiation, or abortive myogenesis. Cross striation in cell and cell cylinders was only faintly indicated by a grouping of cell granules, and a direct transition of cell cylinders with such grouping or initial cross striation into striated muscle fibers was not observed. However, there were many evidences to show that the adult striated

muscle fibers found in this tumor tissue were the end-products of processes of differentiation which the cellular elements had undergone. The presence or absence of cross striation in tumors of this kind is sometimes referred to in the literature as a retention or loss of cross striation. If it is admitted that these tumors are genuine blastomas composed of embryonic tissue, cross striation at a given period has, or has not yet, taken place, but it is not retained or lost. The granular nonstriated tumor cells are at a rudimentary stage of myogenesis, and cross striation simply represents a higher degree of differentiation; i. e., it occeurs later in the transformation of the granular cells into striated muscle fibers.

It has been shown by several writers that muscle tissue regenerating after destruction or injury by inflammation or tumor growth assumes appearances similar to those observed in muscle tumors. Schmincke [6] found that in all vertebrae regeneration of striped muscle is an isogenic process, i. e., it takes place from elements of the old fibers. It is either a continuous process with splitting of the fibers and budding of the ends, or a discontinuous regeneration, namely, from sarcoblasts which develop from the nuclei of the old fibers. The latter process represents cases of extremity, i. e., cases in which all the old fibers are completely destroyed and only some contractile substance with nuclei is left. In such cases the embryonic type of muscle development by sarcoblasts is resorted to. Other investigators, including Galleotti,[7] Weber,[8] Kraske,[9] Waldeyer [10] and Hoffman,[11] believe that the latter type of muscle regeneration is the one which usually takes place, and that the old fibers perish entirely in the regeneration of muscle. According to Abrikossoff, the process may

---

6. Schmincke, A.: Die Regeneration der quergestreiften Muskelfasern bei den Säugetieren, Beitr. z. path. Anat. u. z. allg. Pathol. **45**:424, 1909.

7. Galleotti, G., and Levy, G.: Beitrag zur Kenntnis der Regeneration der quergestreiften Muskelfasern, Beitr. z. path. Anat. u. z. allg. Pathol. **14**:272, 1893.

8. Weber, O.: Ueber die Neubildung quertreifter Muskelfasern, in besondere die regenerative Neubildung derselben nach Verletzungen, Virchows Arch. f. path. Anat. **39**:216, 1867.

9. Kraske, P.: Experimentelle Untersuchungen ueber die Regeneration der quergestreiften Muskeln, Habilitationsschrift, Halle, 1878.

10. Waldeyer, W.: Ueber die Veränderungen der quergestreiften Muskeln bei der Entzündung und dem Typhusprozess, sowie über dei Regeneration derselben nach Substanzedefekten, Virchows Arch. f. path. Anat. **34**:473, 1865.

11. Hoffman, C. E. E.: Ueber die Neubildung quergestreifter Muskelfasern, inbesondere beim Typhus abdominalis, Virchows Arch. f. path. Anat. **40**:505, 1867.

also be reversed; i. e., the preexisting striated muscle fibers lose their transverse and longitudinal striation, then become transformed into granular bands and finally break up into cells with a granular protoplasm. I observed such a breaking down of muscle fibers into cells with a granular protoplasm in a tongue involved in marked granulomatous infiltration which caused extensive destruction of the muscle fibers. Figure 7 shows an area in which the muscle fibers are broken up into granular cells which have a remarkable resemblance to the cells in the tumor presented here, but very essential elements, the nuclei, are almost entirely lacking.

As to the etiology of rhabdomyoma of voluntary striped muscle, the remains of embryonic muscle tissue may be considered, as misplaced embryonic tissue obviously is the origin of the heterotopous rhabdomyomas. There was clearly such an origin in Pendl's and Rütz's cases of congenital rhabdomyoma of the tongue. In adults such tumors of the tongue may appear to be acquired, trauma being an etiologic factor; this organ is also particularly subject to injuries of various kinds. Then, too, in these cases the condition may develop from germs of embryonic muscle tissue which was separated from its physiologic connection, or which for some reason failed to differentiate like the rest of the tissue. Trauma then is only an exciting factor that stimulates the dormant tissue to proliferate.

SUMMARY

Rhabdomyoma of the tongue appears to be relatively the most frequent of rhabdomyomas of voluntary striped muscles. It is a more or less circumscribed, but not encapsulated, benign growth.

The most characteristic microscopic feature of such tumors is large cells with a light protoplasm containing numerous fine granules, and a relatively small nucleus located in the center. These cells correspond to embryonic myoblasts.

A grouping of the granules in stripes, or initial cross striation, was observed here and there in single cells and cells of cell cylinders.

Phases of embryonic myogenesis were represented in syncytium formation, fusion of cells forming cell cylinders and various stages of differentiation in the development of young muscle fibers.

The muscle fibers in the tumor tissue are newly formed and not remnants of preexisting muscle.

There were not any evidences to prove that this growth was rather a regenerative process than a genuine neoplasm.

December 13, 1926.

ANTEROMEDIAN MERO-ACRANIA (NOSENCEPHALOS)

COMBINED WITH HYPOGASTROSCHISIS DEXTRA AND MALFORMATION OF FINGERS AND TOES: REPORT OF A CASE

ERNST PRIBRAM
Professor of Pathology in the University of Vienna, Assistant Professor in Rush Medical College; Pathologist, St. Elizabeth's Hospital
CHICAGO

In the male fetus of a primipara, aged 19, the length of the cord was 3 inches (7.6 cm.); the length of the fetus, 13 inches (33 cm.); the height of the trunk, 7 inches (18 cm.), and the circumference of the chest, 6 inches (15 cm.).

Fig. 1.—Front view of fetus.

The appearance of the skin was normal; the lanugo and hairs of the head were well developed. The vault of the head was not closed, and the brain was expelled during delivery. The parietal and frontal bones were absent. The facial part of the skull presented an open cavity. The face consisted of the upper maxillary arch and mandible. The upper palate was well developed; the

Fig. 2.—Back view of fetus.

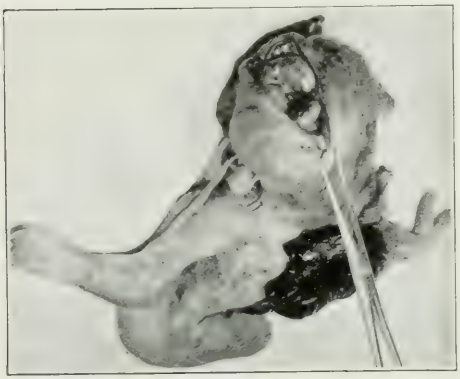


Fig. 3.—Face with tongue.

tongue was present. The meatus auditorius externus sinister was open; behind the latter the external ear was overdeveloped with an adhesion stretching from the upper part of the deltoid region of brachium. The right ear was overdeveloped and fairly normal. There was a sharp bony projection in the region of the left eye. The left eye presented a small aperture with an overdeveloped upper lid and no lower lid. The region of the right eye was covered by epidermal tissue. The maxilla was hypertrophic; there was no cleft palate and no lips; the dorsal part of the wall of the palate was everted anteriorly. The thyroid and cricoid cartilages were well developed. There was a skin appendage on the neck, about 1 inch (2.5 cm.) in length.

The right side of the abdominal wall was open. The liver, small intestines and right kidney were extra-abdominal. The sternum and ribs on the left side

Fig. 4.—Roentgenogram of fetus.

were well developed; beginning from the vertebral column, the right side was curved markedly caudally (fig. 4). The right forearm was bent backward; the hand had only two fingers and both were overdeveloped. The left scapula was present, the left arm was well developed and from the middle of the arm there was an adhesion to the left ear. The adhesion consisted of a cord of skin. The left hand had three fingers, all overdeveloped; the thumb and middle finger were connected, and the middle finger was long and thick.

The opening of the abdominal wall was 5 cm. in length, the umbilicus was open, and the abdominal organs (liver, kidney, gallbladder, small intestine) were everted at the right side and extraperitoneal; the transverse colon was visible and covered by peritoneum. The penis was overdeveloped, and the testicles were not descended.

The length of the right thigh was 2 inches (5 cm.); the left thigh, 2½ inches (6.2 cm.); the right leg, 2 inches (5 cm.); the left leg, 2½ inches (6.2 cm.). The right foot had the shape of a clubfoot and was inverted and adducted; there were four toes—the first and second were firmly connected. The left foot had a normal position; it had five toes, and four of them were enveloped by a common skin and had no end phalanges. The fifth presented all the phalanges and was covered by a nail.

COMMENT

There were three different monstrosities in the fetus: cranioschisis, hypogastroschisis and malformations of the extremities. The cranioschisis was of the anteromedian type: both the parietal and the frontal bones were almost entirely lacking. The hypogastroschisis connected with a partial thoraco-omphaloschisis was continued into the chest, but only as far as the skin was patent; the lungs and ribs were compressed by the eventration of the hypogastric organs, caused by the arrest of the closure of the lateral abdominal wall. There was another resemblance to a thoraco-omphaloschisis—that was the fixation of the right arm to the thoracic wall. Similar cases have been reported by Ballantyne.[1]

The underdevelopment of the right thigh and right leg may have been the consequence of the diminished blood supply caused by the eventration of the abdominal organs.

Both the cranioschisis and the hypogastroschisis were of ectodermal origin, probably early in the embryonic life. The malformation of the fingers and toes is reported in many cases of acranias, but the determining factors are not yet known.

The shortness of the cord may have been the cause of the wrong development during fetal life (between the second and third weeks); but it is not easy in this case to separate the causes from the effects.

December 13, 1926.

BILIARY TRACT PROTOZOIASIS

FRANK SMITHIES

In 1917, my interest in biliary tract protozoiasis was aroused by finding viable *Lamblia intestinalis* (Stiles, 1902) or *Giardia intestinalis* in the bile of a gallbladder removed by Dr. A. J. Ochsner. It seems that this was the first observation of *Giardia* in the human gallbladder, and it was reported before the American Gastro-Enterological Association in May, 1920 (Proceedings: discussion of report by John C. Hemmeter).

Since 1917, gallbladder and bile tract fluids have been examined on a warm stage of the microscope, in hanging drop or slide preparations, for further

1. Ballantyne: Manual of Antenatal Pathology: The Embryo, New York, William Wood & Co., 1905.

instances of protozoan infestation; and since 1921, search has been made for protozoa and other intestinal parasites, in material secured by the duodenal tube, during bile tract drainage, according to the Lyon method or its modifications.

This report concerns thirty-three instances in which protozoa were demonstrated in bile-containing fluids secured from the duodenum after stimulation of the mucosa by a warm 33 per cent water solution of magnesium sulphate. It was not possible, in any instance, to obtain from the duodenum, material containing protozoa, prior to the introduction of magnesium sulphate solutions.

The identification of the protozoa is given in the *Medical Clinics of North America*, 1917. The fresh warm material is examined on the heated stage of a microscope. Encysted forms of the parasite should be noted carefully, especially when endamebae are present. Mixed infestations are not uncommon. Sometimes the parasites are demonstrated by the first examination, but they may be found only after several trials.

In the thirty-three patients, protozoa were found as follows: *Chilomastix mesneli*, 23; *Endamoeba histolytica*, 11; *Endamoeba coli*, 1; *Trichomonas intestinalis*, 4; *Giardia (lamblia) intestinalis*, 2.

Single infestations were: *Chilomastix mesneli*, 18; *Endamoeba histolytica*, 5; *Giardia intestinalis* 2, and *Trichomonas intestinalis*, 1; while concomitant infestations were: *Chilomastix* and *Endamoeba histolytica*, 4; *Trichomonas* and *Endamoeba histolytica*, 1; *Trichomonas* and *Endamoeba coli*, 1; and *Trichomonas, Chilomastix* and *Endamoeba histolytica*, 1.

The thirty-three infestations were found during the examination of 1,591 patients, an incidence of 2 per cent. A recent study of alimentary tract protozoiasis in 3,780 patients demonstrated parasites in 265, or 7 per cent. It seems likely that the careful examination of duodenal fluids for protozoa will demonstrate a greater incidence than this report mentions.

Seventeen patients had lived in or visited southern states or countries; sixteen lived in rural sections of Ohio, Illinois, Idaho and Kansas, of which eleven had travelled in subtropical or tropical regions, and of these four had bloody diarrhea while abroad. People who live in the North and who visit tropical or subtropical regions appear more susceptible to bile tract protozoiasis than do those who have always lived in southern regions and who may be chronic protozoa carriers.

In this series, there were sixteen females and seventeen males, the youngest patient a boy of 8 years and the oldest a woman of 66.

In twenty-nine, cysts or vegetative forms of protozoa were found in the stools — cysts more often. When protozoa were found, some biliary tract inflammation was present.

A surgical removal of the gallbladder was performed in eight patients in whose duodenal fluids protozoa were found. In the contained fluids protozoa were demonstrated, of the kind found in the duodenal fluid. These protozoa were *Endamoebae histolytica*, 6; *Chilomastix*, 1; *Giardia*, 1. In five instances *Chilomastix* was associated with *Endamoebae histolytica* and in one patient *Trichomonas* with *Endamoeba histolytica*. In two gallbladders there was empyema; in two, stones, and in four, catarrhal cholecystitis with regions of edema and ulceration. Acute changes were noted especially in the gallbladder of a *Chilomastix* carrier.

When vegetative forms of *Endamoeba histolytica* infest the bile tracts, lesions similar to those in the bowel may be expected. If cysts only occur, the host may be a harmful carrier. The cysts may be discharged from the biliary tract, and give rise to vegetative forms in the bowel that cause ulcers. It is not possible to enumerate the changes caused by the presence of the flagellates in the bile tracts, but removing them seems beneficial to the patient. The gall-bladder and bile passages as local foci for reinfestation should not be overlooked.

December 13, 1926.

ADENOMA OF THE PARATHYROID

CHESTER C. GUY

A woman, aged 29, with a tumor of the neck for six years, had symptoms of pressure from a growth that seemed to be in the left lobe of the thyroid. This mass was removed at the Cook County Hospital. The tumor was 8 by 6 by 4 cm., encapsulated, and had a cortex of soft, yellow lobulated tissue, and a medulla of necrotic, partly calcified tissue. Microscopically the cortex contained epithelial cells resembling those of the parathyroid. The diagnosis was adenoma of the parathyroid.

The patient returned ten months later with three nodular swellings in the neck in the position of other parathyroid glands. These were thought to be a compensatory hyperplasia rather than metastases of the tumor which was removed.

DISCUSSION

DR. H. JAFFÉ: The diagnosis of a parathyroid tumor should be made with extreme caution. Parathyroid hormone can be demonstrated in mice with a suitable extract of the tumor.

December 13, 1926.

ANEURYSM OF THE RENAL ARTERY

HARRY A. SINGER

Although an aneurysm of a renal artery is manifestly uncommon, it occurs far more frequently than the collected statistics dealing with the subject suggest. The discrepancy between the actual number reported and the number so listed is due mainly to the lack of uniformity in titles, for not an inconsiderable number of reports are made under headings which express the cause, such as periarteritis nodosa, or the effect, as perirenal hematoma, of a renal aneurysm. On this account many reports which rightfully should be included are inadvertently omitted in summaries designated as "aneurysm of the renal artery."

The following two reports are of particular interest in that they illustrate the value of microscopic examination in determining the presence of a renal aneurysm when the etiology is obscure.

Case 1.—A woman, in the late fifties, without apparent cause had a sudden pain in the right loin followed by hematuria. By cystoscopic examination it was determined that the blood came only from the right kidney. After repeated attacks of pain and hematuria had markedly impaired the health of the patient, surgical intervention seemed advisable. A perirenal hematoma was found, and because the source of hemorrhage was not demonstrable, a nephrectomy was performed. The kidney was sent to Dr. R. H. Jaffé, who found by careful dissection a periarterial hematoma which had its origin in a perforation of one of the interlobar branches of the renal artery. The opening in the vessel communicated with a major calyx on one side and the perirenal tissues on the other. Grossly, the main renal vessel showed the usual changes of atherosclerosis, while the kidney itself had the characteristic changes of arteriosclerotic atrophy. In microscopic preparations of cross-sections of the artery opposite the rupture, the intima was practically normal, but the media was greatly altered. The latter had twice the normal thickness and was irregular in structure, the smooth muscle fibers being distributed in various planes and separated by considerable fibrillar connective tissue. Elsewhere there were no noteworthy changes. It was clear from the microscopic examination that the important factor in the perforation was an alteration of the media. Because of the meager history, it was not possible to account for the vascular changes, but they were presumably due to a previous infectious disease, probably nonsyphilitic.

Case 2.—A white woman, aged 46, complained of recurrent attacks of severe abdominal pain and persistent vomiting. She had an abdominal mass on the right side, extending posteriorly to the loin. A rapid and continued increase in size suggested that active hemorrhage was occurring. The flow of urine from the right kidney was diminished, as was determined by cystoscopic examination. In the absence of trauma a preoperative diagnosis of perirenal hematoma of undetermined etiology was made. By a surgical operation an extensive perirenal hematoma was demonstrated. It was caused by a perforation of the right renal artery at a place just distal to its origin from the aorta. To control the hemorrhage while removing the kidney, it was necessary to clamp the artery where it was ruptured and to divide the vessel distal to the defect. Grossly, the extirpated kidney was not changed except for recently clotted blood about its convexity and the presence of a rather firm, grayish-red material which was thought, at the time, to be organizing blood. The larger renal vessels had a patchy intimal sclerosis, although the smaller radicals were unchanged. The portion of the vessel containing the perforation was not removed during the operation. Microscopically, the changes in the sections of the firm tissue found at the root of the kidney were remarkable. The alterations consisted of cellular infiltrations and granulation tissue involving the fat of the hilum together with numerous peculiar vascular structures. These vessels had walls of various thicknesses, some a single layer of endothelium, others moderately thick concentric layers af healthy tissue, while still others were exceedingly thick, and many were slightly or markedly altered by fibrinoid necrosis. The changes here were interpreted as being due to a subacute or chronic inflammation, the source of which is uncertain.

Of particular interest in connection with the reports presented is the etiology. For purposes of classification the causes of an aneurysm of a renal artery may

be traumatic and nontraumatic. The latter group can be further subdivided into primary disease of the arterial wall, either degenerative (arteriosclerosis) or inflammatory (syphilis, periarteritis nodosa), and secondary, due to the extravascular disease. Trauma is the cause of an aneurysm of the renal artery in approximately 50 per cent of the reports on record. With many of these the accompanying arteriosclerosis is an important factor, and the trauma, which often is insignificant, is only the exciting cause.

January 10, 1927.

SKIN REACTIONS WITH COCCIDIOIDAL GRANULOMA

EDWIN F. HIRSCH

From the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago, Ill.

Broth culture and synthetic medium filtrates of *Coccidioides immitis* injected in animals infected with *Coccidioides immitis* and in a patient with coccidioidal granuloma, cause reactions in the skin resembling those occurring with tuberculin in tuberculous animals. The immediate reaction of the skin is like an urticarial wheal; the delayed reaction is a red swelling of the skin, at its maximum usually within from twenty-four to forty-eight hours after the injection. Heating at 80 C. for thirty minutes does not destroy the activity of these filtrates. Two volumes of 95 per cent alcohol added to one of the filtrate flocculates a substance with active properties that can be dried and powdered. It contains from 3 to 4 per cent nitrogen and, on hydrolysis, from 20 to 40 per cent reducing sugar measured as dextrose.

A complete report is published with Harriet Benson and Dorothy D'Andrea in the *Journal of Infectious Diseases* **40**:629, 634, 638, 1927.

January 10, 1927.

ACUTE INTESTINAL OBSTRUCTION IN A NEW-BORN INFANT FROM HERNIA OF THE LOWER ILEUM THROUGH A CONGENITAL MESENTERIC OPENING

ESMOND R. LONG

University of Chicago

Intestinal obstruction from herniation of part of the bowel through a congenital mesenteric opening has been described as "unusual but not rare." Anatomists refer to the condition without mentioning specific instances. Both Treves and Davis in their textbooks on anatomy state that occasionally congenital defects are found in the mesentery, through which part of the bowel may slip with subsequent strangulation. The most recent report on the anomaly is that of G. D. Cutler (*Boston M. & S. J.* **192**:305, 1925), who reviewed twenty-seven reports of this disorder and added one of his own.

All of these came to the attention of surgeons as typical intestinal obstruction, with a history of three or four days, as a rule, of pain, vomiting and

obstipation. The exact nature of the obstruction was not correctly diagnosed in any patient before operation. The age incidence of the patients varied from 1 to 70, the condition occurring more often during youth and a few times in infancy. Operation disclosed herniation of from a few inches to several feet of bowel through slitlike openings, usually close to the ileocecal junction, varying from $\frac{5}{8}$ of an inch to 3 inches (1.5 to 7.6 cm.) in length, with strangulation or volvulus. Bloody fluid was found in the peritoneal cavity in all patients, and frequently the strangulated bowel was gangrenous. The operative aim was either reduction or resection. In spite of operation in the cases reviewed, the mortality was over 50 per cent. In general, the mesenteric defects were believed to be of congenital origin, although there was a history of trauma in a fourth of the cases.

The subject of this report was a boy, aged 4 days, a patient of Dr. J. P. Graf at St. Bernard's Hospital. The infant was born of a normal mother, in an easy, normal delivery. It was noted at the time of birth that the infant had a peculiar "froglike" shape. The abdomen was abnormally large, and the thorax was abnormally wide at its junction with the abdomen. The baby took the mother's breast readily, receiving a little water in addition to colostrum from the breast. No bowel movements occurred. The night nurse thought she recollected one passage of meconium, but was uncertain; in view of the condition of the colon found at necropsy, it was almost certain that no meconium ever passed. The abdominal swelling increased, and on the third day castor oil and an enema were given, but had no effect. Following every attempt to nurse after this, the child vomited. A diagnosis of intestinal obstruction, possibly intussusception, was made, and an operation was performed on the fourth day. The peritoneal cavity was found to be full of bloody fluid, and a large loop of bowel without mesentery was seen. The prognosis seemed hopeless, and as the infant was almost moribund, the wound was closed without further manipulation. The child died two hours later.

Necropsy was performed the same day. The abdomen was greatly distended, and the thorax was short, with a broad base, having the configuration of a short cone. There was a slight icterus. Except for these abnormalities and the laparotomy incision, there were no important external changes. Internal abnormalities were found only in connection with the alimentary tract. The peritoneal cavity contained bloody fluid. The stomach and duodenum were normal. The upper jejunum was normal, except for hemorrhage between the leaves of the mesentery. The lower jejunum and upper ileum were enormously dilated and filled with salvelike, green meconium. For a length of 30 cm. the average circumference of the bowel in this location was 15 cm. The ileum tapered gradually to normal size at the lower end of the dilated part. Beginning 15 cm. below the most dilated portion there were numerous fenestrations of the mesentery along a bowel length of 15 cm., extending to within 4 cm. of the ileocecal junction. The last 35 cm. of ileum had passed through one of these openings and was twisted. The coils of this part were drawn tightly together and were almost empty. The entire colon was collapsed and was free from meconium. Smears of the meconium from the distended part disclosed the typical gram-negative flora of the new-born infant before establishment of the mother's milk supply.

The cause of the fenestration which permitted the hernia with volvulus and intestinal obstruction could not be determined with certainty. In view of the peculiar configuration of the infant's abdomen with pressure deformity of the thorax, noted at birth, it may be assumed that the obstruction took place during intra-uterine life. Whether the fenestration resulted from an embryonic defect or intra-uterine tearing it was not possible to determine. Certainly trauma had added to the extent of fenestration during or after birth, because normal development of the intestinal wall could not have occurred with such extensive loss of mesentery and blood supply as was found at the necropsy. Probably the extreme distention and stretching of the bowel as a result of the obstruction had added to the tearing of the delicate mesentery, with hemorrhage, leading to the hemoperitoneum noted.

It is interesting to speculate on the effect of intestinal obstruction before and after the advent of bacteria in the bowel. Possibly the bacterial flora, which developed after food and water were taken by mouth, played a part in the symptoms attending the intestinal obstruction.

January 10, 1927.

HEMOCHROMATOSIS AND PRIMARY CARCINOMA OF THE LIVER

D. K. HIBBS

From the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago

Primary carcinoma of the liver associated with cirrhosis is relatively common and seems to occur with the pigment type of cirrhosis more often than is recognized generally. Karsner's review (*Arch. Int. Med.* **8**:238 [Aug.] 1911) mentions cirrhosis in all livers with a primary carcinoma, and of the 107 reports of primary carcinoma of the liver reviewed by Winternitz (*Johns Hopkins Hosp. Rep.* **17**:143, 1916), cirrhosis was present in 87 per cent. Rowen and Mallory (*Am. J. Path.* **1**:677, 1925) reported nine primary carcinomas of the liver in 6,506 postmortem examinations. Seven of the nine carcinomas were of the liver cell type, and six of these occurred in livers with marked cirrhosis. The cirrhosis in three cases was of the pigment type, in three others the alcoholic type. Rowen and Mallory believe that a progressive necrosis of liver cells is accompanied by regeneration, which finally results in cells proliferating indefinitely, as in a malignant tumor.

The cases of three of the sixteen patients with hemochromatosis examined postmortem at the Boston City Hospital during the last twenty-six years are reported by Mills (*Arch. Int. Med.* **34**:292 [Sept.] 1924). These patients are said to have died because of a coincident primary carcinoma of the liver, a sequence which he considers to be relatively frequent. These lesions arise, according to Mills, because of the continual necrosis and regeneration of liver cells, which finally exceed their normal growth limits and proliferate

as a carcinoma. Blanton and Healy (*Arch. Int. Med.* **27**:406 [April] 1921) report hemochromatosis in four patients, one of whom had a primary carcinoma of the liver.

M. H., a white man, aged 64, was brought to St. Luke's Hospital, Chicago, in an ambulance. He seemed well until the afternoon of admission, when he suddenly collapsed while at work and became unconscious. At the time of admission he had symptoms of a cerebral hemorrhage or thrombosis, and he died on the following day. The postmortem examination (by Edwin F. Hirsch) showed that death was due to a huge spontaneous intrapontile hemorrhage. A pigment cirrhosis and a primary carcinoma of the liver, with tumor tissue thrombosis of branches of the portal vein near the carcinoma were also found. The liver with the empty gallbladder weighed 2,900 Gm. It was dark red-brown, with a capsule finely nodular and roughened by depressed regions of fibrous tissue. The substance of the liver was leathery. On surfaces made by cutting, the lobular markings generally were obscured, and the tissue contained yellow-gray nodules, 4 to 6 mm. in diameter, of regenerating liver parenchyma. Near the center of the right lobe was a gray mass of tissue about 6 by 8 cm. with irregular prolongations which on surfaces made by cutting appeared as discrete nodules of tissue. One margin of this mass was beneath the liver capsule on the front surface. A dilated branch (4 by 2 cm.) of the portal vein adjacent to the tumor was filled with gray tissue 5.5 cm. long. Histologic preparations of the gray mass contained carcinoma tissue with an arrangement into papillary structures having a delicate fibrous stroma and suggesting an origin from duct epithelium. There was a pigment cirrhosis of the liver tissue itself. Deposits of brown pigment like those of the liver were present also in the pancreas, in the suprarenal glands and in the biliary lymph nodes. Hemofuchsin and hemosiderin granules were demonstrated in these tissues according to the method suggested by Mallory, Parker and Nye (*J. M. Research* **42**:461, 1921). A chemical analysis of 350 Gm. of liver tissue fixed in formalin failed to demonstrate copper. However, since the tissues had been kept in formalin for about a year before the chemical analysis was made, the copper compounds may have been dissolved.

While many details regarding the past history of this patient could not be obtained, it is known that he used alcohol excessively, and for over ten years had worked as a tradesman on metal lamps.

January 10, 1927.

PARASITIC NODULES RESEMBLING TUBERCULOSIS IN THE LUNGS OF SWINE

L. ENOS DAY

JOHN S. BENGSTON
AND
H. B. RAFFENSPERGER

Nodules caused by parasites in the lungs of swine occur often, and closely resemble miliary tubercles. So close is this resemblance that often the two varieties of nodules are distinguished macroscopically with difficulty. This

distinction is important, because the final disposition of the carcass depends on which of these diseases is present. For many years it has been known that palisade worms in the lungs of certain animals cause nodules. As early as 1875, Bugnion *(Compt. rend. de la réunion de la Soc. Helvétique a Andermatt,* 1875) divided verminous pneumonia in sheep caused by *Synthetocaulus rufescens* into three types, the third form of which he designated as nodular pneumonia. The nodules range in size from that of a millet seed to that of a pea, and are either grayish yellow or dark red, according to the acuteness of the inflammatory process. This, he says, is the commonest form, and the nodules are infiltrations of the tissue caused by the ova and embryos in the alveoli. Gratia, in 1883, reported similar nodules in the lungs of swine, an observation confirmed by others.

In January, 1923, a portion of the lung of a hog with a large number of pleural nodules resembling miliary tuberculosis was received for examination from the meat inspection station at Madison, Wisconsin. Histologically, the nodules were unlike tuberculous lesions, and consisted essentially of lymphocytes arranged in small, grapelike clusters. A satisfactory interpretation was not made at that time, but later more swine lungs with similar lesions were found by inspectors in the Federal Meat Inspection Service in Chicago.

In several sections from one of these nodules were found portions of parasites containing eggs with larvae. The eggs of lung worms in swine are known to contain larvae before they are extruded by the parasite. These observations, later confirmed, established the causal agent of the lesions.

In their migration along the bronchi the lung worms sometimes penetrate the minute bronchioles, and die. They act as a foreign substance which stimulates a hyperplasia of the lymphoid tissue and the formation of the nodules.

The bronchi of the posterior parts of the lungs are more frequently infested with lung worms than those in the anterior parts, and parasitic nodules also are more frequently found in the posterior lobes, as demonstrated by the examination of 11,429 lungs of swine.

Metastrongylus elongatus occurred in the lungs of swine in relation to *Choerostrongylus pudendotectus* in the ratio of 31:7. *Choerostrongylus pudendotectus,* when present, was always associated with *Metastrongylus elongatus. Metastrongylus salmi* was not observed.

Of the twenty-three lungs with parasitic nodules containing disintegrating parasites, five contained both species, and eighteen had only *Metastrongylus elongatus* in the bronchioles. Of the forty-six lungs with nodules in which parasites were not demonstrated, thirty-eight contained *Metastrongylus elongatus* only, and eight contained both parasites. Of the fifty-five lungs without nodules, forty-one contained *Metastrongylus elongatus* only, and fourteen contained both parasites.

It seems, then, that *Metastrongylus elongatus* causes the nodules described in the lungs of swine, possibly also *Choerostrongylus pudendotectus,* but since lungs with the latter parasitic infestation alone were not found, definite conclusions may not be reached from the results of our investigations.

The complete report will be published in the *Journal of the American Veterinary Medical Association* for 1927.

February 14, 1927.

A LARGE HYPEROSTOSIS OF THE CRANIUM DUE TO ARACHNOID FIBROBLASTOMA, MALLORY (SO-CALLED DURAL ENDOTHELIOMA)

S. M. CROWE

John J. Borland Fellow in Medicine

AND

C. K. JONES

From the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago

Hyperostosis of the cranium with endothelioma of the dura has been reviewed by Cushing (*Arch. Neurol. & Psychiat.* **8**:139 [Aug.] 1922; *Brain* **45**: 282, 1922), Penfield (*Neurol. & Psychopath.* **4**:27, 1923; *Surg. Gynec. & Obst.* **36**:657, 1923) and others. It is not an unusual condition, although according to Cushing, its occurrence in the first two decades of life is rare. His statistics indicate that these tumors, which he chooses to call meningiomas, occur in a ratio of about 1:4 to the gliomas. These meningiomas comprise about 10 per cent of the verified tumors of the brain and in about 25 per cent of them there is an accompanying localized thickening of the cranial bone. More than once the exostosis has been considered the primary new growth and has been removed, the symptoms returning after a time, as reported by Spiller (*J. A. M. A.* **49**:2059 [Dec. 21] 1907). The bony swelling has recurred also, as reported by Rand (*Arch. Surg.* **6**:573 [March] 1923), and although it was removed a second time, it has reappeared, and the underlying tumor has been removed only at the third operation.

J. J., a schoolboy, aged 16, was admitted to St. Luke's Hospital as a patient of C. K. Jones and E. W. Ryerson on March 3, 1926, with a bony tumor of the forehead. Eleven years before he had fallen down a short cellar stairway, striking his forehead on the cement floor. Two weeks later a small, smooth lump was noticed, and it was considered by a physician to be a hematoma. For three years, there was no appreciable change in the size of the lump, and then when the boy was 8 years old it started to grow, painlessly and symmetrically. During the last three years there had been little change in its size, except that the mother thought that there had been definite growth for several months before he entered the hospital. The boy had had repeated epileptiform attacks since the age of 10. The first seizures, occurring during a period of two days as repeated spastic convulsions, were considered due to dietary indiscretions. The second attack, a year later, was characterized by loss of consciousness and falling to the floor, as was the third a month later. After three years, at the age of 15, the boy had three short convulsions in one week, the first following a heavy meal. One year later, in January, 1926, he had two short convulsions, one lasting three minutes, the other only a minute or two. Since then the mother had noticed that her son on two or three occasions apparently lost consciousness for a moment or so. He did not fall, but seemed "absent." A playmate had noticed the same thing. The patient was unconscious during all of the attacks, and they occurred without warning. In each instance there was rigidity during the seizure and severe headache following it, relieved according to the mother, by a dose of castor oil. There was a history

of considerable gastro-intestinal disturbance from infancy through childhood, and of asthmatic attacks since the age of 8. Besides the usual diseases of childhood, the patient had had bronchopneumonia, pleurisy and erysipelas.

During the examination at the hospital little was found except the swelling of the forehead. Results of a previous roentgen-ray examination were reported by Hollis E. Potter as follows: "There is an enormous laying down of new bone, suggestive of an osteoma, apparently not penetrating beneath the lower table." Neurologic examination by G. W. Hall disclosed no organic disturbance of the central nervous system. The patient was alert, and there was no mental deterioration.

At the operation, noted by an intern "to be one of mental therapeutics and cosmetic," an "osteoma of the frontal bone" was sawed off. The tumor was symmetrical with respect to the midline of the skull, and the periosteal covering was adherent to it and about ⅜ of an inch (0.96 cm.) thick. Results of the roentgen-ray examination ten days after the operation were reported by E. L. Jenkinson as follows: "The large osteoma involving the frontal bone has been removed. The internal table is intact except for a small area about 1½ inches (3.77 cm.) above the glabella."

Eleven months after the operation the boy is apparently well, is an honor student in high school, and is a member of the school swimming team. He has been taking phenobarbital, supposedly, every day since the operation, and he has not had any more convulsions. In recent roentgenograms there is no noteworthy change in the shadows of the cranial bone. Vision and eyegrounds are normal.

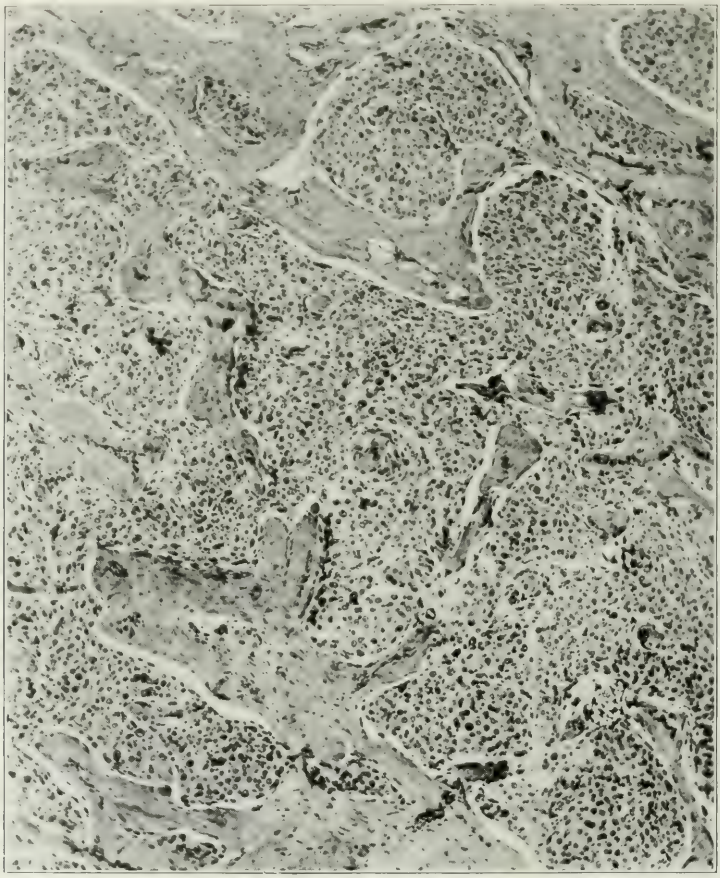
The tissue removed at operation was examined by Edwin F. Hirsch, who reported the following observations: The three pieces of compact bone were 9 by 3.3 cm., 9 by 3.5 cm., and 9 by 4.5 by 2 cm. They seemed to have been cut from a roughly spherical mass. On the surfaces that had been sawed there was hard, bony, tissue-like cortex; the parts on the outside were porous, and some were covered with a little closely adherent fibrous tissue. With these was a roughly wedge-shaped piece of fibrous tissue 9.5 by 3 by 1 cm. The three pieces of bone together weighed 156 Gm.

Sections of the fibrous tissue (the periosteal covering) contained dense masses of hyaline fibrous tissue and collagen. Between the fibrous septums were masses of large polygonal cells, which in the hematoxylin-eosin stain had a faint purple cytoplasm and a vesicular round nucleus. These in places were arranged concentrically, some around small blood vessels. In sections of the bone there were similar masses of these cells in the large marrow spaces. With special stains, such as phosphotungstic acid-hematoxylin, Weigert's elastic tissue and aniline blue, the specific staining qualities of the collagen and elastic fibers were demonstrated. These staining reactions and the histology permitted the diagnosis of a so-called "dural fibroblastoma."

Comment.—According to Cushing, the view that a "dural fibroblastoma" arises from the arachnoid, was first expressed by John Cleland, of Glasgow, in 1864, and similar opinions were later given by C. Robin of France (1869), by Schmidt (1902) and by Weed and Cushing (1915). Mallory (*J. M. Research* **41**:349, 1920) published a histologic study with the statement that there is no dural endothelium, and that the tumors commonly considered as arising from such a structure in reality develop from the growing cells of the arachnoid.

Two years later, Cushing discussed the origin from the arachnoid, the favored places of occurrence and the factors in the development. As factors he considers age, congenital predisposition, trauma and the physiologic activity of the cells of the arachnoid concerned. He considers the relation to trauma close and more than coincidence.

The tumor is not known to metastasize (Towne: *Ann. Surg.* **83**:321, 1926), although it may invade the dural sinuses and may extend through the cranium



Photomicrograph illustrating structure of a tumor; × 75.

and into the scalp and temporal muscles. It may displace and compress brain tissue, but according to Mallory, "it cannot pass through the arachnoid from which it has risen and invade the brain."

Microscopically, Mallory describes the arachnoid fibroblastoma as composed of cells that are usually large and more or less flattened, but sometimes spindle-shaped, often having a marked tendency to wrap themselves about each other, around strands of connective tissue or around blood vessels, forming

concentrically arranged masses of cells or whorls of various sizes. The cells may be arranged in a palisade effect. The whorls may be fibrous. With slow growth fibroglia, collagen and elastic fibrils may be formed.

The manner of growth of the hyperostosis has been studied by Phemister (*Arch. Surg.* **6**:554 [March] 1923). He believes that the tumor stimulates the production of new bone which is itself not tumorous. The pad of tumor tissue between the hyperostosis and the scalp has been described by Penfield.

The tumor may exist without symptoms, the manifestations depending on the size and location of the intracranial growth. The bony swelling, when present, may or may not be painful or tender. Convulsions, either generalized or localized to one part of the body, have been reported repeatedly. Headache is probably even more frequent, and in the cases reported by Penfield it was of a stabbing or neuralgic character, rather than of the increased intracranial pressure type. Hemiplegia, eye changes and mental disturbances are less commonly observed.

It is Cushing's opinion that "unquestionably many of these lesions are never recognized during life and even if a diagnosis of tumor suspect be made, localization may be extremely difficult in the absence of hyperostosis, palpable or shown by the roentgen-ray." Sosman and Putnam (*Am. J. Roentgenol.* **13**:1, 1925), reviewing the roentgenograms of ninety-five verified intracranial meningiomas, found in nearly half of them recognizable changes characteristic of the tumor, but in discussing the differential diagnosis they state that it may not be possible to distinguish between osteoma and the tumor except by operation.

The treatment of patients with arachnoid fibroblastoma is surgical. As stated by Cushing, the tumor may increase in size without giving evidence of its growth, so that the operation for its removal may be most formidable. Cushing, Penfield and others have called attention to the fact that the tumor apparently does not recur locally when a little is left, either in the muscles of the scalp or at the attachment to the dura. Both report the cases of patients who were well twelve years after operation. Sosman and Putnam, however, mention five patients operated on a second time, one as long as nine years later, for recurrence of the tumor.

February 14, 1927.

MICROSCOPIC CHANGES IN SICKLE CELL ANEMIA

I. PILOT

My interest in sickle cell anemia (Herrick) was aroused by recognizing the disorder in tissues of a young negro in whom the disease was not recognized clinically. The tissue changes are so definite that this peculiar anemia may be identified without difficulty in microscopic preparations. The recorded descriptions of tissue changes are limited, there being only four based on examination of tissues at autopsy. These reports were made by Huck, Graham and Sydenstricker. I shall mention the essential features of the disease in another patient.

A negro, aged 16, entered the Cook County Hospital complaining of pain in the ankles and knees, malaise and anorexia of one week's duration. He said that about ten days before he had had a "cold," and three days later he had

felt pain in the left ankle. Pains in the knees and in the lumbar region appeared on the following day. Profuse sweats occurred several times. Similar attacks of pain and sweats occurred two weeks prior to the present attack, and similar attacks had been noted before. He had had a chancre four months before and had received six "injections."

Physically, the boy appeared ill; his temperature was 101.8 F., his pulse rate, 112, and his respirations, 24 per minute. The head presented patchy alopecia and the skin contained macular patches, especially on the forehead, the palms and extremities. The sclerae were markedly icteric. The lips were fissured, the teeth were good, and the tonsils were large. The lungs were resonant; the heart had a systolic blow at the apex. The abdomen was tympanitic, the liver extending two fingerbreadths below the costal arch. There was a healing chancre on the shaft of the penis, a marked tenderness about the knee and ankle, but no swelling or edema. All the lymph nodes were moderately enlarged and hard. A clinical diagnosis of secondary syphilis and icterus due to arsenic therapy was made. The patient's temperature rose to 105 F.; he became more toxic, and died within forty hours after admission. The urine contained albumin. The Wassermann reaction was reported 4 plus.

The anatomic diagnosis showed: macular rash of the skin, icterus, bilateral fibrous pleuritis, caseated and calcified tuberculosis of the parabronchial lymph nodes, petechial hemorrhages of the epicardium, slight sclerosis and bile staining of the aorta. The thymus was 7 cm. at the base; the spleen weighed 150 Gm., and the capsule was thickened and wrinkled. On surfaces made by cutting there was a marked increase of the connective tissue, with peculiar raised gelatinous regions that stood out prominently. The liver weighed 2,800 Gm. It was soft, light brown, and the markings were obscured. The kidneys were enlarged, the left weighing 270 Gm. and the right 250 Gm. The capsule was stripped with difficulty, and depressions were left on the surface. The markings were fairly clear. The suprarenals were normal in size and contained little lipoid in the cortex. The bone marrow was red in places. The pancreas, prostate and urinary bladder were unchanged.

The spleen was markedly hyperemic and hemorrhagic. The trabeculae were thickened and contained large quantities of brown and yellow pigment, most of which gave a positive iron reaction. Often there were associated calcium deposits. There were only small islands of lymphoid tissue. About the pigment and calcium deposits was an occasional foreign body giant cell. The pulp was densely packed with bundles of sickle-shaped red blood cells. The sinuses were lined by endothelial cells without phagocytosis. There were many sickle-shaped red cells within the sinuses, together with a few macrophages containing iron pigment and phagocytosed red cells.

The sinuses of the liver were distended with round and sickle-shaped erythrocytes. There were many coiled masses of sickle cells which were large Kupffer cells crowded with phagocytosed red cells. The cords of the liver cells were narrow and contained fat, but there was no iron-containing pigment. The reticulum was distinctly increased, and the capillaries slightly thickened.

The vessels of the kidney were engorged, and the capillaries of the glomeruli were prominent. Bowman's space was narrow. The epithelium of the convoluted and collecting tubules contained large deposits of iron-containing pigment. The interstitial tissue was slightly increased and infiltrated with a few round cells.

The lymph nodes had dilated sinuses in the medulla and poorly developed follicles in the cortex. The capsule and the trabeculae were thickened. The sinuses contained many phagocytic endothelial cells with engulfed round and sickle-shaped red cells. A small amount of iron-containing pigment was present under the capsule.

The bone marrow had many regions of erythropoesis and granulopoesis. The sinuses were filled with nucleated erythrocytes and occasional nucleated sickle cells. There were numerous sickle cells, together with various types of immature and mature myelocytes. Megokaryocytes were abundant. Numerous macrophages packed with phagocytosed red cells, many of the sickle cell type were present in the sinuses.

In the myocardium there was a slight edema, fragmentation of the fibers, dilated vessels and no pigment. The thymus did not contain any noteworthy changes. The lungs were unchanged except for engorged capillaries, but there was no phagocytosis by the endothelium.

The distinctive changes noted in the examination of these tissues were the marked distention of the vessels with many sickle cells, the marked phagocytosis in the liver, lymph gland and bone marrow and the large deposits of iron-containing pigment in the spleen and kidneys. Hemorrhages had occurred frequently in the spleen, and these tissues especially were changed. The histologic changes observed in the tissues mentioned corresponded closely with those observed by R. H. Jaffé in the tissues of two other patients in whom sickle cell anemia was recognized clinically.

DISCUSSION

R. H. Jaffé.—In sickle cell anemia the erythroblasts and normoblasts in the bone marrow appear morphologically normal. The transformation of the erythrocytes to sickle cells takes place in the organs of the reticulo-endothelial system, especially in the spleen. The sinuses of the spleen contain only sickle cells, while in the peripheral blood, from 4 to 40 per cent of the red cells are disfigured. The sickle cells are phagocytosed by the Kupffer cells of the liver and by the reticulo-endothelial cells of the abdominal lymph nodes. Phagocytosis practically does not occur in the spleen.

The anatomic changes in sickle cell anemia resemble those found in hemolytic jaundice.

February 14, 1927.

OSTEITIS DEFORMANS (PAGET'S OSTEITIS, OSTEO-DYSTROPHIA FIBROSA SENILIS [CHRISTELLER-FRANGENHEIM])

R. H. JAFFÉ

The clinical history of this patient is interesting because of the connection between trauma and the onset of the disease. A woman, aged 83, fell on her right knee twenty years ago while alighting from a street car. Since that time she had noticed a swelling of the injured knee, which gradually extended over the right thigh. Later the tibia and the left lower extremity became affected.

The patient was bedridden for fifteen years. In the last five years the upper arms started to swell. She died of angina pectoris.

Autopsy demonstrated an enormous deformity of the lower extremities. The circumference of the right thigh was 52 cm., that of the left, 87 cm. Both femurs resembled a watermelon in size and shape. The weight of the right femur was 6 Kg. The cross diameter in the middle of the diaphysis was 16 cm. The histologic changes were typical of osteitis fibrosa. There was a dense net-

Fig. 1.—Roentgenogram of the right femur.

work of osteoid tissue trabecula with little calcification and many osteoclasts. The bone marrow in the peripheral parts of the diaphysis consisted of a loose fibrillar connective tissue with accumulations of round cells and many mast cells. The hyperemia of the marrow, a characteristic which has been emphasized by Pommer and F. J. Lang, was marked. In the center of the diaphysis and in the epiphysis fatty marrow was found. It contained much myeloid tissue, the myeloid metaplasia apparently being due to infections that had started from ulcerations of the skin about the deformed bones.

Besides the femurs, both tibias and the lower end of each humerus were involved in the process.

The parathyroids microscopically had the structure found in aged persons. There was no hyperplasia. Calcium metastases were observed in the convoluted tubules of the kidney and in the lymph vessels about the inguinal lymph glands.

The following anatomic changes were found in the other organs: scirrhus carcinoma of the right breast, bilateral hemorrhagic bronchopneumonia, marked sclerosis of the coronary arteries, chronic fibrous myocarditis, atrophic cirrhosis of the liver, chronic cholecystitis, cholelithiasis and chronic diffuse nephritis—

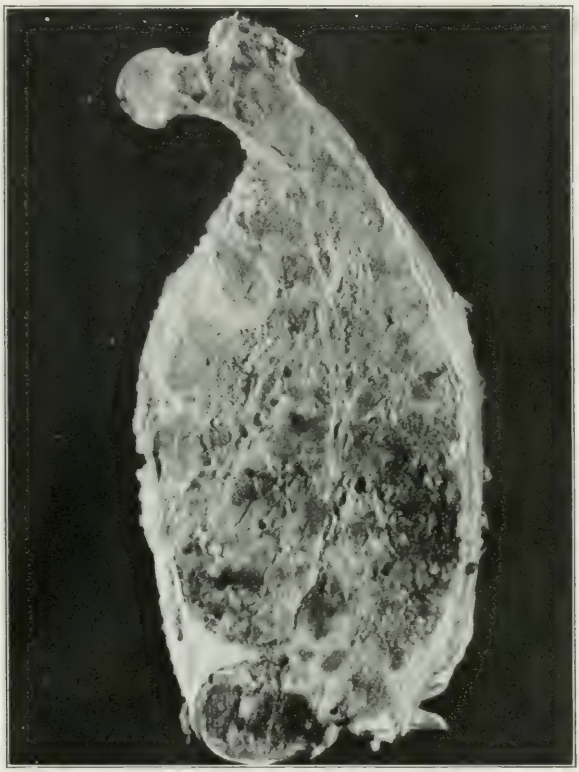


Fig. 2.—Transverse section of the right femur.

primary contracted kidneys, right nephrolithiasis and marked atheromatous sclerosis of the abdominal portion of the aorta.

February 14, 1927.

A FIBROMYXOMA OF THE ENDOCARDIUM

EUGENE F. TRAUT

A retired merchant, aged 76, an inmate of the Versorgungsheim der Gemeinde Wien, had a condition diagnosed clinically as cerebral apoplexy. There were no symptoms of cardiac insufficiency, and he died thirty-six hours after the

hemorrhage. The anatomic diagnosis (Professor Jacob Erdheim) was hemorrhage into the left hemisphere with rupture into the ventricles. The heart changes were incidental and played no part as a cause of death.

The external appearance of the heart was normal. A longitudinal incision through the left side disclosed a pedunculated round tumor as large as a small hen's egg attached to the upper border of the foramen ovale and hanging into the left auricle (fig. 1). Its greatest diameter was 4.5 cm., and the pedicle attaching it to the septum atriorum was 2.5 cm. thick and 1 cm. long. The tumor was dark red with patches and streaks of yellow on the sides. The pedicle was gray. The surface most distant from the pedicle was roughened. There the tumor had a fibrinous attachment to the opposite wall of the auricle.

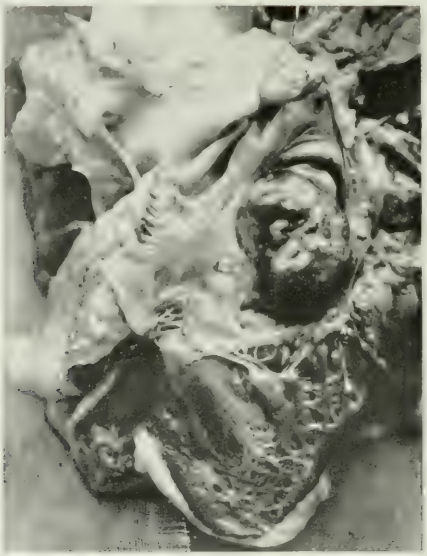


Fig. 1.—Photograph of the tumor in situ.

At the attachment of the pedicle, the septum was 1 cm. thick. Palpation of the tumor gave the sensation of a bag filled with pebbles. It was so flabby that on a flat surface it flattened out. Not far from the base of the tumor was a firm, gray prominence 4 mm. wide and about 3 mm. high, roughened with fibrin.

The wall of the left auricle was moderately hypertrophied. The heart had no other gross abnormalities. There were no scars or mural thrombi. On cut surfaces the mass had a red and yellow mottled appearance as noted externally. Sections taken from several parts were stained with hematoxylin and eosin, van Gieson's stain, Weigert's stain for elastic tissue, the Berlin blue stain for iron pigment and the Unna-Pappenheim stain for plasma cells.

The mass (fig. 2) consisted of edematous connective tissue with small middle-sized vessels consisting of endothelium alone and occasionally a small layer of elastic tissue. Hemorrhages were scattered here and there. The

distribution of hematogenous pigment was more extensive. There were great collections of phagocytes filled with hemosiderin. Spindle cells were infrequent, and those present did not contain pigment. The cell bodies were absent in many places, but the fibrils persisted. Meyer's stain for mucin failed to give a positive reaction anywhere in the tumor. Hyaline degeneration was present in many places. A considerable part of the mass was made up of infiltrated cells, lymphocytes and plasma cells occurring separately or together. In the most extensive regions of infiltration, the lymphocytes were crowded into the

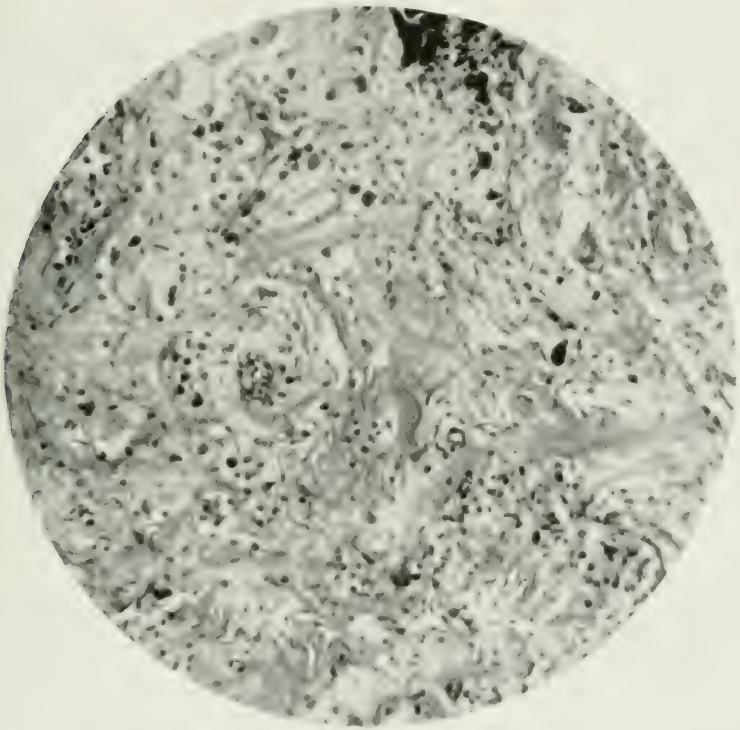


Fig. 2.—Section from the interior of the tumor (hematoxylin and eosin) showing the loose connective tissue structure, phagocytes filled with hemosiderin, and plasma cells.

center. The plasma cells lay along the periphery. Among them were numerous Russell bodies, additional evidence of a chronic inflammation. Hemosiderin accumulations were especially marked in the vicinity of the infiltrations. Small deposits of calcium were present in the hyalinized regions.

The elastica stain demonstrated that the tumor contained much elastic tissue. The elastic fibers were irregularly divided and were especially thick near the surface and surrounded the larger vessels. Elastic fibers also enclosed round and oval masses of mononuclear cells in the interior. The shape of these cells varied, corresponding most nearly to lymphocytes and plasma cells.

A thick layer of hyalinized connective tissue, with scattered regions of calcification formed the surface of the tumor. Only in the pedicle did elastic tissue form the outer layer of the tumor.

The appearance of the septum varied with the part examined. In one place the endocardium was slightly thickened and infiltrated with lymphocytes and plasma cells as well as a few wandering cells containing pigment. The myocardium underneath had a moderate amount of fibrous tissue, infiltrated with lymphocytes and plasma cells.

In a place not far removed, the endocardium was markedly thickened; there was hyaline degeneration but no infiltration. In another place the endocardium was covered with a white thrombus, and at one place the fibrin was 3 mm. thick, hyalinized and partly calcified. The free surface of the thrombus was covered with a layer of fibrin containing red and white corpuscles. In contrast to the appearance of the pedunculated mass, the organization of this thrombus had progressed very little by infiltration with a few spindle cells, but without vessels. The thrombus had no elastic fibers in spite of its attachment to the elastic endocardium. The myocardium contained a small amount of fat. Both the endocardium and the myocardium seemed to extend a short distance into the pedicle of the tumor.

Tumors of the endocardium are uncommon. Most often they are like the one described, being fibrous, pedunculated structures arising from the soft fibrous tissue in the subendothelial layer of the endocardium, and then usually occur in the auricles. More have been described on the left than on the right side of the auricular septum. The margin of the foramen ovale is a favorite site of attachment. Of course, congenital anomalies are common in this region. Berthenson (*Virchows Arch. f. path. Anat.* **132**:390, 1893) and after him Albrecht considered these growths among the malformations, structures arising from fetal rests.

Forel and others regard them as pseudoneoplasms. Forel considered them simply organized thrombi, pointing out that they occur in the auricles, the favorite site of mural thrombi. According to Forel and his followers, the connective tissue fibers are the organizing tissue.

Against this view and in favor of the neoplastic origin of the growths is their flabby consistency and the lobulation. A thrombus as large as these tumors could never be organized through a narrow pedicle. An organizing or organized thrombus contains at least in parts, deposits of fibrin, usually hyalinized. Fibrin is absent in my tissue except for a thin layer on the capsule. The buffeting in the blood current explains the hemorrhages in the interior of the tumor. Elastic tissue is rare in organized clots but abundant in the sections of this mass. Endocardial tumors usually are found accidentally during postmortem examination. Among their commonest manifestations are multiple emboli in the systemic circulation. I believe that this pedunculated mass of the left ventricle is a tumor.

DISCUSSION

Edwin F. Hirsch: There is a close resemblance between this tissue and tissue of inflammatory origin. The genesis of this mass may be like that of nasal polyps.

E. F. Traut: Professor Erdheim considers the mass to be a tumor.

March 14, 1927.

CHANGES AT THE ORIFICES OF THE INTERCOSTAL ARTERIES IN A DISSECTING ANEURYSM OF THE AORTA

N. F. FISHER

From the Norman Bridge Pathological Laboratory of the Rush Medical College of the University of Chicago and the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago

A report by Crowell (*J. A. M. A.* **77**:2114 [Dec. 31] 1921) contains a review of dissecting aneurysms of the aorta and records four more. In an analysis of 215 such aneurysms, he states that in more than 90 per cent the changes were either marked fatty and fibrous plaques or advanced sclerosis with ulceration. In about 9 per cent these alterations were slight. The age of most of these patients is 40 years or more, but it ranges from 13 to 95 years. The ascending portion of the aorta was involved most frequently and other parts of the aorta in order with decreasing frequency.

The primary rupture is of the intima. This may extend through most or all of the media, because the dissection occurs between the media and the adventitia, or in the outer layers of the media. The branches of the aorta may be dissected or even cut across at their origins. The pressure on the branches of the aorta may cause marked circulatory disturbances. Crowell says that little attention has been given to such interference of the circulation, a disturbance which alone may cause symptoms. Disregard of these symptoms may be responsible for the failure to recognize dissecting aneurysms of the aorta during life.

Case 1.—A woman, aged 64, was admitted to Washington Boulevard Hospital (S. R. Slaymaker), May 5, 1926 at 1:45 p. m. She complained of severe pain in the region of the heart and between the shoulders. The temperature was 98.8 F., pulse rate 80 and respiration 20; the heart was enlarged and the beat irregular but without murmurs. After morphine and a digitalis preparation were given, the patient slept and was fairly comfortable. At 9:00 p. m. she complained of a severe pain between the shoulders; she died after twenty-five minutes.

Necropsy (R. D. Evans).—Syphilitic sclerosis and dissecting aneurysm of the aorta; left hemothorax; compression atelectasis of the left lung; blood staining of the tissues of the posterior part of the mediastinum; detached parietal pleura of the upper part of the left pleural cavity; slight bilateral passive hyperemia and edema of the lungs; fatty changes of the pulmonary arteries; cyst of the left ovary; multiple calcified fibromyomas of the uterus; calcified peribronchial lymph node (healed tuberculosis?); right fibrous pleuritis; coal pigmentation of both lungs; diverticula of the jejunum; polyp of the cervix uteri; cholecystocolic ligament.

The aorta was 63 cm. long. The lining of the first 10 cm. was smooth, except for a large irregular, yellow, elevated plaque 2 cm. in diameter and a few similar ones, as large as 5 mm. in diameter. The lining of the aorta elsewhere was roughened throughout by irregular plaques or wrinkled, ulcerated and eroded regions. There was a transverse slit 1 cm. in length, 2 cm. distal

to the root of the innominate artery. A similar transverse opening 1.5 cm. long was noted about 1 cm. further. Both openings extended through the intima and the media to communicate with an aneurysmal sac. A probe could be passed distally between the coats of the aorta for several centimeters.

Beginning at the upper border of the junction of the innominate artery and the aorta, there was a dissecting aneurysm which involved the entire circumference of the aortic wall for a distance of 8 cm. In the next 13 cm., the aneurysm was from 2 to 3.5 cm. wide and involved the left intercostal arteries and in the next 9 cm. down to the renal arteries, the entire circumference of the aortic wall was dissected, except for a narrow region about 6 to 10 mm. wide on the posterior wall. One centimeter proximal to the opening of the superior mesenteric artery was a transverse slit 0.9 cm. wide, surrounded by an atheroma which connected the intramural space with the lumen of the aorta. There were several small blood clots here. Adherent to the wall of the aorta, just below the innominate artery was a mass of mediastinal fat and a sac, communicating with the intramural space in the aorta. The sac contained freshly clotted blood.

All of the intercostal arteries were present, except the eighth on the left side which probably was congenitally absent. A 2 mm. probe could be passed into each intercostal artery. The lumen of each of the arteries on the left side was reduced in size, especially of the second, third, fourth and sixth intercostals, whose lumen was reduced to 1 mm. or less. The lumen of the first, second, third, fourth and ninth intercostals on the right side was reduced, especially of the fourth and ninth arteries. The aneurysm surrounded the first, second, third, fourth and fifth intercostal arteries on the right side, and all on the left.

Histologic sections were taken transversely to the intercostal arteries at their junctions with the aorta. These were made at different levels to determine the extent to which the different layers in the walls of the intercostal vessels were involved as well as to estimate the size of their lumens.

Dickenson (*Tr. Path. Soc. London* **13**:48, 1862), McCallum (*Bull. Johns Hopkins Hosp.* **20**:9, 1909), Barhat (*Arch. Heilk* **13**:473, 1872) and Todd (*Tr. Med. chir.* **17**:301, 1844) have reported cases in which certain paralyses could be explained easily on the basis of interference with the blood supply to the spinal cord. In others, as those of Adami (*Montreal M. J.* **24**:945, 1895) and Edwards and Stone (*Tr. Path. Soc. Philadelphia* **6**:38, 1878) a similar explanation would seem satisfactory for the abdominal pain. In the latter, usually the clinical diagnosis of "surgical abdomen" is made, and an abdominal operation is performed.

The patient whose case is reported here had severe pain, especially in the left side of the chest and between the shoulders. The microscopic examination demonstrated a marked decrease in the size of the lumens of the second, third, fourth, and sixth left intercostal arteries, and it seems probable that thoracic pain in this patient was due to interference with the blood supply. The segmental distribution of the intercostal vessels to the spinal cord offers a satisfactory explanation for pain limited to certain regions or for paralysis of a particular part.

March 14, 1927.

TOTAL PERSISTENCE OF THE RIGHT AORTIC ARCH

A. ARKIN

The complete report is published in Wien. Arch. f. inn. Med. **12**:385, 1926.

A HUGE CONGENITALLY CYSTIC LIVER AND CYSTIC KIDNEYS

EARL O. LATIMER

From the Normal Bridge Pathological Laboratory of the Rush Medical College of the University of Chicago and the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago

Congenital cysts, although not common, are met often enough clinically to be considered in the diagnosis of tumors of the liver. They have been a pathologic curiosity for many years because of the size of the liver, the theories of origin and other features. Congenital cysts of the kidneys are far more common.

The first theory as to the origin of cysts of the liver of this type seems to have been advanced by Förster (cited by Moschcowitz to be referred to presently), who thought they were dilated bile ducts. He believed that the bile ducts had become occluded by an inflammation and as a result had become dilated because of retained bile. Among others sharing similar views are Cornil and Ranvier (Pathological Histology, trans. by Shakespeare and Simes, Philadelphia, 1880, p. 565), Forbes (*St. Bartholomew's Hosp. Rep.* **33**:181, 1897) and Blackburn (*Tr. Path. Soc. London* **55**:203, 1904).

Sabourin (*Arch. de physiol. norm. et path.* **10**:62 and 213, 1882) carefully studied two cystic livers and in one found cirrhosis; therefore he concluded that the cysts were caused by the cirrhosis. He believed that they were new epithelial growths, formed from newly formed bile ducts and called them "angioma biliare."

Siegmund (*Virchow's Arch. f. path. Anat.* **115**:155, 1889) objected to the inflammatory theory, and suggested that they are true cystadenomas. However, he did not state whether they were formed from bile ducts or liver cords. Hippel (*Virchow's Arch. f. path. Anat.* **123**:473, 1891), speaks of cystadenomas formed from bile passages that were originally present. Nauwerck and Hutschmid (*Beitr. z. path. Anat. u. z. allg. Pathol.* **12**:1, 1893), and v. Kahlden (*Beitr. z. path. Anat. u. z. allg. Pathol.* **13**:291, 1893) also called them cystadenomas, while Dmochowski and Janowski (*Beitr z. path. u. z. allg. Pathol.* **16**:102, 1894) called them fibro-adenomas. The latter workers found cystic livers in connection with cystic kidneys, and, believing that the latter were true tumors, presumed that the cysts of the liver also were true tumors.

Still (*Tr. Path. Soc. London* **49**:155, 1898) was the first to express the opinion that they had their origin in embryonal maldevelopment. Moschcowitz (*Am. J. M. Sc.* **131**:674, 1906) studied the cysts carefully and agreed with Still. Moschcowitz says, "non-parasitic cysts of the liver are associated with congenital anomalies in other parts of the body especially with cysts of the kidney.

Such cysts of the liver are always associated with congenital anomalies of the liver, consisting in aberrant bile ducts, which may be extrahepatic or intrahepatic. These aberrant ducts are embryonal 'rests,' formed in the course of development of the liver, and have thus far been found only in cystic livers or livers associated with cystic kidneys. Non-parasitic cysts of the liver have their origin in these aberrant ducts and may assume two forms: one, arising from inflammatory hyperplasia of these ducts; the other, by retention of fluids in these ducts, as a result of congenital obstruction. There is no valid reason for classifying these cysts among tumors."

Borst (Borst, cited by Moschcowitz) combined the idea of a tumor with that of congenital origin. He brought forth the view that in the complicated process of embryonal development the relation of the growth of epithelium to connective tissue was disturbed. However Borst later told Meyenburg (*Beitr. z. path. u. z. allg. Pathol.* **64**:477, 1918) that he no longer placed as much stress on the adenomatous character as he formerly did. Borrmann (*Bibl. Medica* **13**:1, 1900) Muller (*Virchow's Arch. f. path. Anat.* **164**:270, 1901), and Vorpahl (*Beitr. z. path. Anat. u. z. allg. Pathol.* **53**:477, 1912), saw no adenoma changes.

Meyenburg subscribing to the double embryonal origin of the liver as expressed by Lewis (Keibel and Mall: Handb. d. Entwicklungsgesch des Menschen. Leipsig, 1911, p. 391) conceived of the cysts originating in bile passages of the first order. In the liver of a child who had congenitally cystic kidneys he found some blind bile passages of the first order that were connected with the parenchyma of the liver but not with the general biliary system. He believed that these were a preliminary stage of cysts of the liver and concluded that the cysts formed because of the failure of some of these small bile ducts to establish their connection with the larger bile passages.

Lorentz (*Frankfurter Zeitschr. f. Path.* **29**:249, 1923) believes that there is a monistic origin of the primary bile passages; but agrees that the damage is done at the time there should be an embryonal reduction of the anastamoses among the bile passages. He failed to find any connection between the blind passages and the liver parenchyma.

Teuscher (*Beitr. z. path. Anat. u. z. allg. Pathol.* **75**:459, 1926) believes the cysts to be due to embryonal malformations, although, she always found openings between the cysts and the bile passages. Therefore, she does not believe their growth is due to a deficient opening; but rather, to a capacity for growth of the epithelium, the cystic development merely being one expression of a perverted tendency, widespread in the body, for the tissues of the excretory ducts to multiply at the expense of more highly differentiated glandular tissue. Sometimes this tendency rests on an anomaly in the germ plasma, suggesting an hereditary tendency for maldevelopment.

After this brief résumé of the theories of origin of congenitally cystic livers, it is the chief purpose of this report to place on record an unusually large congenitally cystic liver, the weight of which, so far as can be learned from other reports, is exceeded by only one other.

In 1906 Moschcowitz was able to collect only eighty-five undoubtedly congenitally cystic livers, all but fourteen in adults. There have been others reported since; but of all these only a few were greatly enlarged. The largest of these livers are listed according to their weights in the following table.

Bland-Sutton (*Brit. M. J.* **2**:1167, 1905) states that congenital cysts of the liver may enlarge the organ until it weighs 35 pounds (16 Kg.). However a careful review of his references fails to reveal a liver of that weight. Boyd (*Lancet* **1**:951, 1913) collected thirty-four instances of nonparasitic cysts of the liver that were treated surgically. Many of these were large single cysts, but there is no record of weights.

History.—A woman, aged 40, entered St. Luke's Hospital, July 3, 1926, in the care of Peter Clark because of a swelling of the abdomen and a

Greatly Enlarged Congenitally Cystic Livers (Arranged According to Their Weight)

Reported by	Liver Weight	Measurements	Kidneys	Year
Dmochowski and Janowski (Beitr. z. path. Anat. u. z. allg. Pathol. **16**: 102, 1894)	10,850 Gm.	40 cm. broad 33 cm. thick 18 cm. long	Cystic	1894
Latimer*	8,806 Gm.	36.5 cm. broad 30 cm. thick 14 cm. long	Cystic	1927
Vorpahl (Beitr. z. path. Anat. u. z. allg. pathol. **53**: 477, 1912)	8,181 Gm. (18 pounds)	40 cm. broad 33 cm. thick 17 cm. long	Cystic	1912
Courbis (These de Paris, 1877: cited by Forbes)	8,000 Gm.	.....	Cystic	1877
Kaufmann (Speziellen Path. Anat. Berlin **1**: 609, 1911)	7,130 Gm.	.....	.....	1911
MacDonald (New York State J. Med. **8**: 185, 1908)	6,350 Gm. (14 pounds)	.....	.....	1908
Rolleston (Diseases of the Liver, New York, 1912, p. 499)	6,095 Gm. (13 lb. 7 oz.)	.....	.....	1912
Meyenburg (Beitr. z. path. Anat. u. z. allg. Pathol. **64**: 477, 1918)	5,870 Gm.	.....	Cystic	1918
Kaufmann (Speziellen Path. Anat. Berlin **1**: 430, 1896)	5,500 Gm.	.....	.....	1896
Roberts (Am. J. M. Sc. **108**: 664, 1894)	5,227 Gm. (11.5 pounds)	.....	.....	1894
Sharkey (Tr. Path. Soc. London **33**: 168, 1882)	2,954 Gm. (6.5 pounds)	.....	.....	1882
Siegmund (Virchow's Arch. **115**: 155, 1889)	2,610 Gm.	.....	.....	1889
Blackburn (Tr. Path. Soc. London **55**: 203, 1909)	2,386 Gm. (5.25 pounds)	.....	Cystic	1904
Patterson (Brit. M. J. **2**: 1316, 1891)	2,197 Gm. (4 lb. 13.5 oz.)	.....	.....	1890
Bristowe (Tr. Path. Soc. London **7**: 229, 1856)	1,992 Gm. (4 lb. 6.25 oz.)	.....	.....	1856

* This report.

feeling of stiffness and tightness in the lower thoracic and in the epigastric regions. She was able to be around, but worried about an abdominal mass which first was noticed eleven years before as a small nodule in the right nipple line just below the costal border. Shortly after the birth of her last child, three years before, this mass began to grow rapidly. When admitted to the hospital the liver was hard and nodular and extended to the umbilicus in the midline, a little lower on the right side and a little higher on the left

side. The patient was not jaundiced but had soft clay-colored stools. Syphilitic hepatitis, echinococcus cyst and congenitally cystic disease of the liver were considered. On July 10, 1926, an exploratory operation was made by Peter Clark. The liver was greatly enlarged and studded with cysts, the kidneys were cystic also. A small piece of tissue, removed at the operation, was diagnosed congenitally cystic liver. The patient died on July 20, 1926.

The laboratory results were normal for the blood, the urine, and the feces except for clay-colored stools. The blood Wassermann test was negative.

Postmortem Examination (Edwin F. Hirsch).—The liver was a large multicystic mass weighing 8,806 Gm. (19.5 pounds). In its maximum dimensions it was 36.5 cm. broad, 30 cm. thick and 14 cm. long. About 90 per cent of the superior surface consisted of closely set cysts, the largest 8 cm. in diameter, the smallest several millimeters. The walls of the cysts were tensely distended with clear, faintly yellow fluid making the surfaces exceedingly nodular. On the superior surface only three irregular regions could be identified as liver parenchyma. They were about equal in size and finely mottled brown to purple. Many of the cysts were confluent and multilocular. The anterior border was irregular, and about 14 cm. to the right of the midline was a region stained with bile about 3 to 4 cm. (biopsy wound) and involving the border and inferior surface about equally. In the center of this was a torn place 1.5 by 1 cm. The tissue exposed was stained yellow-brown with bile, rough and slightly edematous. The inferior surface was like the superior except for two larger cysts placed one on each side, and immediately adjacent to the interlobar fissure, 10 by 9 by 7.5 cm., and 8.5 by 8 by 7 cm. They were opposite each other and near the anterior border. On the surfaces made by cutting, in a frontal plane from below through both lobes at once, a quantity of clear fluid escaped. About 90 per cent of these surfaces were composed of the cysts, which were confluent, multilocular and present throughout the entire substance of the liver. The parenchyma of the liver where present was red-brown and there was a moderate cloudy swelling. The lobular markings were only moderately distinct. The lining of the cysts were smooth, glistening white, with fibrous connective tissue strands in a network. The thickness of the cyst walls varied from 1 to 3 mm. irrespective of the size of the cyst.

The right kidney weighed 1,320 Gm. and was 22 by 14 by 8.5 cm. It was, like the liver, a multilocular mass, roughly cresentric in shape. About 95 per cent of the anterior surface was covered with closely-set cysts, varying in size from 2 mm. to 5.5 cm. in diameter. There was a small amount of yellow lobulated fat on the outer surface of the pelvic region. The color of the cysts varied from amber to purple blue. The parenchyma of the kidney was gray-red and contained many pinhead-sized cysts. The posterior surface was like the anterior, except that 20 per cent of it was covered with yellow lobulated fat in a thin layer in the region of the pelvis. The kidney capsule stripped with difficulty, many superficial cysts being torn in the process, leaving the kidney substance gray-red and smooth. On the surfaces made by cutting, many cysts were opened and the contained fluid escaped; the color of this fluid varied from pale straw to chocolate, according to the color of the cyst. It was estimated that altogether this kidney contained about 2 per cent of the parenchyma of the kidney. This had a moderate cloudy swelling, and the cortical markings were lost.

The left kidney weighed 890 Gm. and was 20.5 by 11.5 by 8 cm. It was like the right kidney, except that no parenchyma was recognized. On surfaces made by cutting, the characteristics of the cysts were like those of the liver and the other kidney.

Histologic Examination.—Around the central vein of the liver, the cell columns were narrowed and the sinusoids widened and distended with blood cells in about one third of the lobules. In several other sections, this was less marked. There were two kinds of cysts: smaller ones, ranging in size from about that of the central vein to about 1 mm. in diameter and having a wall made up of several layers of fibrous tissue only; larger ones, ranging in size from that of the central vein (of which there were only a few) to 5 to 6 mm. in diameter (of which there were many), and having a fibrous tissue wall which was lined by a single layer of cuboidal epithelium making up about one fifth of the thickness of the wall. All contained a homogeneous coagulum. The larger cysts were irregularly placed, the smaller were uniformly in the region of the portal triad. The smaller kind of cysts were surrounded by normal liver tissue, the others by a narrow zone of necrotic tissue just outside of the capsule. Altogether about thirty sections from twelve different regions were studied.

March 14, 1927.

VARIATIONS IN THE TUBERCLE PARASITE

H. C. SWEANY

In former reports (*J. A. M. A.* **87**:1206 [Oct. 9] 1926 and *Am. Rev. Tuberc.* **14**:523, 1926), there was uncertainty as regards the interpretation of the observations then recorded. As the result of these and further studies, the monomorphic idea of Koch and his followers was questioned, especially as regards its application to the tubercle bacillus. Having been convinced that the tubercle parasite is not always acid-fast and not always a bacillus, I was led to see if there might not be other changes which either have not been observed commonly or perhaps have not been accepted. The monographs of Löhnis (Washington, D. C., Natl. Acad. Sc., Second Memoir, 1922, vol. 16) and Hadley (*J. Infect. Dis.* **40**:1, 1927), and the various papers by Mellon (*J. Bact.* **11**:203, 1926), are recent summaries of these bacterial changes. The incompletely understood work of D'Herelle (The Bacteriophage and Its Behavior, Baltimore, Williams & Wilkins Company, 1926) may also be mentioned. I shall report only what has been observed with the parasite of tuberculosis.

The nonacid-fast granules of the tubercle bacillus have been changed into acid-fast bacilli which are apparently true tubercle bacilli. The process varies widely, depending, presumably, on the source and environment of the granules. Some reproduce by direct fission, with an elongation of the granules; others lengthen without fission; others unfold giving a "coma" appearance when they first emerge, and some of the granules appear to sprout; that is, the new growth is much smaller than the granule, and it actually takes on a motility that lasts a varying time. Many of the granules contain two, three and as many as five germinating centers. Double granules are common. When these sprout they frequently produce a pair of parallel bacilli.

The acid-fastness of these organisms may return promptly or gradually. I have obtained results with various mediums. Hog spleen tissue incorporated

into glycerin agar seems to have a stimulating effect on certain cultures. Petroff's medium without gentian violet is one of the best. When the return of acid-fastness is prompt, frequently an acid-fast coccus or bacillus is joined to the nonacid-fast granule, the newer part taking on acid-fastness. When the return is slower, semi-acid-fast forms of cocci and bacilli with Much granules are seen.

These observations have been accepted rather generally by bacteriologists. Some of the newer aspects of the subject are not so generally accepted, and some have not been presented before, so far as I know. These will be reported as observed, and for the present no conclusions are drawn.

They may be considered as follows:

Degeneration Forms.—These are produced by unfavorable environment, may be semi-acid-fast, may have acid-fast granules or may be wholly nonacid-fast. The size and morphology vary. In fact, it seems that morphology is more a reaction to environment than a specific characteristic. These forms may or may not be tuberculogenic.

Regeneration Form.—These either may be produced artificially, as above, or are found originally in tuberculous lesions. They may be caused to pass back gradually to acid-fastness and, coincidently with this change, the lesions produced in guinea-pigs are like those of tuberculosis.

As further corroberative evidence, I have succeeded in isolating by the single cell method organisms which roughly parallel these in pathogenicity and in staining qualities. A gradual progression of changes seems to take place from the nonacid-fast to the acid-fast, with pathogenic and cultural properties characteristic of each change. Finally, I have been able to isolate from animals, acid-fast organisms that resemble the human form of tubercle bacillus. It is too early to make this statement final, because the animals are still living. These changes have been brought about more frequently in strains of bacteria that at first were atypical. Nevertheless, the final cultures have been so typical in appearance and so different from the ones at the beginning that I wonder if the start was made with an atypical form, which after several animal passages developed into a typically human type. At present, however, I cannot apply this to tubercle bacilli in general, although one of the strains I employed, which at the beginning was a typically human type, after growth on mannite bouillon produced granular forms in one of the guinea-pigs. These granules assumed various shapes as the environment was altered. I do not wish to generalize on this alone. A large number of organisms must be similarly treated and isolated, preferably by the single cell method, as has been done with the nonacid-fast coccoids and diphtheroid-like forms which have reverted to acid-fastness and have tuberculogenic properties.

A definite rule cannot be given for causing these stable strains to vary. The cultures must be obtained in an unfavorable environment. Then search for unusual forms is made, but no prediction can be ventured when these will appear. Placed in celloidin capsules and buried in the peritoneal cavity of guinea-pigs unusual forms have appeared. These changes have been observed and compared by staining, and by dark-field examination. Being unable to photograph the dark-field preparations I must rely on sketches and written descriptions of the changes.

The apparatus used for single cell purification is the one of Janse and Peterfi made by Carl Zeiss, and a suitable moist chamber which guards against contamination, and enables the accurate isolation of single organisms.

Petroff's egg medium without gentian violet has been used. Gentian violet inhibits tubercle bacilli, especially the regenerating forms. A spleen medium consisting of 5 per cent ground and filtered hog spleen added to glycerin agar, a 5 per cent serum and 5 per cent potato added to glycerin agar, and various

other combinations of glycerin, serum and potato with and without agar have been used. Chocolate blood agar is a fair medium for growing tubercle bacilli and also for demonstrating any hemolysis. Various other bouillons and solid mediums have been tried, but plain veal egg mediums rank first. Petroff's medium with gentian violet has little place. Serum mediums, including blood agars of various kinds, are fairly useful; potato medium is less useful. The spleen medium has a tendency to produce anomalous growths but is not recommended for isolating organisms.

The staining methods used have been simple. Good results have been obtained by using simple stains such as Ziehl's, Gram's and a combination of these two in which malachite green is used as a counter stain. All glassware is cleaned in an acid bath, and the stains are filtered before they are used.

DISCUSSION

ERNST PRIBRAM: The tubercle bacillus is a mold related to the actinomyces and accordingly can form a mycelium, bacillary forms or spores. The spores in the tubercle bacillus are difficult to recognize except by staining. Are the red stained portions in the bacilli of the illustration spores or parts of the body? Do these occur in all or just in certain special strains of tubercle bacilli?

H. C. SWEANY: I think the granules are not spores but rather resting stages.

April 11, 1927.

MALIGNANT TUMORS OF THE PITUITARY BODY

E. B. FINK

Because of the interesting clinical syndromes with which they are associated, tumors were the first lesions of the pituitary body to be intensively studied. Most of these are benign. Of the malignant tumors, sarcomas are extremely rare. Benda accepts only one report as a true sarcoma. LeCount, in a discussion of acromegaly, emphasizes the absence of metastases as against the sarcoma nature of many of the tumors associated with acromegaly and reported as sarcomas.

True malignant epithelial tumors of the hypophysis are occasionally encountered and are not rare. They are malignant, just as rapidly growing gliomas are malignant. They grow by infiltration of the brain substance, and are often rapidly fatal but do not produce metastases to distant parts of the body.

There are two types of carcinoma of the hypophysis. One is composed of epithelial cells, usually derived from the chief cells of the anterior lobe. The other, the true nature of which was first established by Erdheim, is a mixed tumor derived from the embryologic pathway of the pituitary body, the so-called "hypophysenganggeschwulst." Many of these contain squamous epithelial remnants of Rathke's pouch, some of them have structures resembling thyroid gland tissue, cartilage and bone. Probably all of these malignant tumors arise from the pituitary stalk, and are extrasellar from the outset.

Four tumors are presented in my report. Two were composed of epithelial cells resembling neutrophil chromophobe cells of the anterior lobe, and extended deeply into the brain tissue as far forward as the frontal lobe. The third was a mixed tumor containing bone, cartilage and epithelial structures resembling thyroid tissue. The fourth was a squamous cell carcinoma. All were suprasellar tumors, probably arising in the pituitary stalk.

April 11, 1927.

THE PATHOGENESIS OF AGRANULOCYTOSIS

HARRY JACKSON

Since 1922, when Werner Schultz first reported the symptoms designated "agranulocytosis," there have been thirty-four reports with the autopsy results from thirty-two patients. Twenty-six patients were from 38 to 65 years old, four were between 17 and 38 and one was a boy 4¼ years old. Most of them were female, only six being male. There was not any history of previous disease. Most of the women were obese, and a number had gallbladder symptoms. One had an alcoholic cirrhosis of the liver; two had had a previous attack from which they had seemingly recovered. The disease seems not to be contagious. Twenty-nine cases occurred in Germany, one in Scandinavia, one in Vienna and three in the United States.

Among the thirty-four patients, pathogenic bacteria were recovered from the blood during life in nine. The pneumococcus and pyocyaneus each were recovered two times, *Staphylococcus aureus* three times and *Bacillus coli* and *Staphylococcus aureus hemolyticus* each once. *Bacillus pyocyaneus* and *Staphylococcus aureus* from two patients, injected into rabbits, caused death in one or two days. *B. pyocyaneus* from another produced a leukopenia in rabbits. These organisms smeared on the throat of animals did not produce any reaction. In most patients the throat during life contained the usual organisms. The bone marrow after death contained *B. coli, B. Pyocyaneus, Streptococcus hemolyticus* and *Staphylococcus aureus* and *albus* once. Many organisms were found in the necrotic places in the throat, and bacterial emboli were found occasionally in the spleen, liver and kidneys.

The characteristic lesions are the gangrenous ulcers of the mucous membranes without granular leukocytes and their precursors in the blood and tissues of the body. The differential blood count demonstrates practically 100 per cent lymphocytes. Ulcers preceded by pseudomembranous inflammation occur in the throat, especially about the tonsils and spread to Waldeyer's ring, the base of the tongue, the larynx, the trachea, the gums, the palate and throughout the intestinal tract. The regional lymph nodes are swollen. The mucous membranes of the vulva, vagina and rectum also are affected. The bone marrow in the long bones is red and has no granular leukocytes and myelocytes. There are numerous nucleated red blood cells and the megakaryocytes are normal. Microscopically, under the necrotic zone of the ulcers, are a few lymphocytes and plasma cells, but no leukocytes. The oxydase reaction in the bone marrow, spleen and other tissue is negative.

The most probable theory of origin is that there is some toxic agent which destroys the hematopoietic power of the bone marrow to produce granular leukocytes. That is, the myeloblasts and myelocytes are destroyed in the bone marrow as well as the adult granular leukocytes in the blood stream. With this natural defense of the body gone, ulcerations of the mucous membranes occur as a secondary phenomenon. The causal agent is unknown. Another theory is that some specific invading organism is the causal agent and gains entrance to the mucous membrane of the throat. A third theory maintains that there is a congenital deficiency of the bone marrow to produce granular leukocytes. The occurrence of the disease late in life disproves this.

A woman, aged 65, previously healthy except for bronchial asthma, had been under daily observation in the hospital convalescing from a fracture of the neck of the femur. Her blood count before becoming sick was normal. She died on the seventh day of her illness. The lowest leukocyte count was 300

cells per cubic millimeter, 92 per cent of which were lymphocytes. The autopsy demonstrated ulcerative lesions in the throat. The bone marrow had only nucleated red blood cells, megakaryocytes and a few eosinophilic leukocytes.

April 11, 1927.

CONGENITALLY CYSTIC KIDNEYS

H. W. TRAUB

Congenitally cystic kidneys in a man, aged 47, of at least twelve years' duration, are reported. The left kidney, which filled the entire right side of the abdomen, was removed with the diagnosis of renal tumor. Its weight after inadvertent bisection and loss of at least a liter of cystic fluid was 3,136 Gm. Many cysts, ranging in size from that of a walnut to that of a hen's egg, were present. The intercystic septums ranged in thickness from that of a bare tissue film to several millimeters. The ratio of cyst tissue to solid intervening tissue was easily 3:1. While no semblance of cortical or medullary marking remained, some sections contained many glomeruli, as well as uriniferous tubules, all with retrogressive changes.

After the left kidney had been removed, the right kidney, which had not been felt, could be palpated, although its mass was much smaller. The phenolsulphonphthalein excretion of the right kidney was 42 per cent.

On the twelfth day after the operation, thrombosis of the right leg occurred. Dry gangrene of the right foot followed, and death occurred sixty-five days after operation, and fifty-three after the onset of the thrombosis. The autopsy (C. W. Fishback) demonstrated a right polycystic kidney, weighing 1,108 Gm. Cystic changes were not found in other viscera. There was an abscess at the upper pole of the right kidney, with fibrous adhesions to the diaphragm; a suppurative pyelonephritis, ureteritis and cystitis, and complete occlusion of the right femoral artery by a thrombus distal to the origin of the profunda femoris. There were various and other changes of no significance in causing death.

April 11, 1927.

THE PURIFICATION AND NATURE OF DIPHTHERIA TOXIN

ARTHUR LOCKE
AND
EDNA R. MAIN

From the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago

Diphtheria toxin may be partially purified by a method of fractional isoelectric precipitation. The toxic and antigenic principles are flocculated from the crude broth filtrate by adjustment of the p_H to 3.3—3.8 with 0.035 normal solution of hydrochloric acid; the sediment is collected by centrifugalization, washed and dissolved in 0.005 normal solution of sodium hydroxide; and the alkaline solution is fractionally precipitated after the addition of salt to isotonicity. Two fractions are obtained, one of which is olive green, flocculates at p_H 5.0—5.2 and contains all the toxic and antitoxin-binding capacity of the original broth filtrate, associated with less than 0.001 mg. of nitrogen per Lf

unit. It is not pure toxin. The other fraction is colorless, flocculates at p_H 4.0—4.06, is nontoxic, nonantitoxin binding, but does precipitate with antitoxin serums. It constitutes more than 50 per cent of the raw precipitate and may be classified as precipitinogen. Both fractions give a mauve biuret, positive Millon, xanthoproteic, Molisch and sugar-reduction reactions. The tests for phosphate and reduced sulphur are negative so far. The chemical and physical properties of the precipitates indicate the presence of a mucin, either as an impurity or as an integral cementing or binding constituent.

May 9, 1927.

CHEMICAL ALTERATIONS IN THE LYMPH DURING BACILLARY SHOCK

WILLIAM F. PETERSEN
AND
GEORGE MILLES

A series of experiments were conducted to investigate further the autonomic balance.

The thoracic duct in quiet, normal animals was incannulated under local anesthetic, and samples of lymph were collected at intervals of from five to fifteen minutes. A saline suspension of *B. coli*, about 5,000,000 organisms per cubic centimeter, was injected continuously by means of a Woodyatt pump at the rate of from 0.5 to 1 cc. per minute after a control period of from one-half to one hour.

The calcium was determined by the method of Kramer and Tisdall, and the potassium by the same method somewhat modified. The proteins were determined refractometrically, and the sugars by the micro-Benedict method.

The ratio of potassium to calcium changed following injection. Most often it dropped, though in a few animals having a low ratio in the control period, the reverse occurred. These minor fluctuations were brought out particularly by determinations made at short intervals and were superimposed on gross changes in the general level which occurred over long periods. The animals had a tendency throughout to return to the original status, and, as is usually noted, to overcorrection. As death approached, this corrective or protective mechanism failed, and a sharp steady drop in the ratio occurred. In some cases this phenomenon was masked by the liberation of potassium into the lymph by hemolyzed red cells.

There is, as would be expected, a distinct relation between the various constituents of the lymph. For example, the ratio of potassium to calcium and the lymph sugar show mirror images of each other in their curves; that is, with the upward trend of the one a corresponding drop is noted in the other, a relationship which often persists even until the death of the animal. Occasionally an animal was found in which this was reversed.

Similarly, the concentration of the lymph as indicated by the lymph proteins tended to mirror the ratio of potassium to calcium, and here, as before, an occasional animal showed a reverse reaction.

The carbon dioxide in general tended to drop as the experiment proceeded, indicating a progressive acidosis, but with each sharp rise in the ratio—i.e., an increase in the lymph potassium, usually absolute—the value of the carbon dioxide rose.

The urine regularly ceased flowing with a sharp rise in the ratio, and the flow was resumed with a fall, especially in the early periods when the animal still had sufficient resistance to recover. In one instance blood appeared in the urine with the final drop. A drop in the ratio occurred with the onset of a chill, and it rose with the end of the chill.

On the basis of these experiments and in the light of previous work, we have concluded that the presence of a low potassium-calcium ratio in the lymph (one below 1.75) is associated with a high degree of permeability in the visceral organs, as is indicated particularly by the passage into that fluid of such large molecules as those of the proteins. In other words, this is a state of visceral parasympathetic orientation or activity during which the permeability does not exceed the bounds of recovery. A high ratio is indicative of a sympathetic status, that is, decreased permeability.

With the break occurring in the recovery mechanism of the animal an irreversible change in the balance and more or less permanent injury to the organism result. At the same time a rapid increase in permeability occurs, the potassium-calcium ratio drops, and, since at this place the liver is exhausted of sugar, the lymph sugar drops. In the animals that still have available sugar, however, it rises sharply.

May 9, 1927.

A CASE OF AGRANULAR BRONCHONOCARDIASIS

RUTH TUNNICLIFF
AND
HARRY L. HUBER

From the John McCormick Institute for Infectious Diseases

Within the past few years there have been numerous reports of unusual infections of man with higher bacteria, and we wish to present one we have studied for more than two years.

The patient, Rose G., aged 21, a native of Sicily, was brought to America by her parents during her eighth year. She had always been well, but at the age of 14 she had had a respiratory infection which was diagnosed as pneumonia. After recovery she was well, but, as she did not gain in weight, tonsillectomy seemed to be indicated. During the operation, under ether anesthesia, at her home, she revived sufficiently to tear away all instruments and had to be held forcibly until ether was administered again. Following this, she had a high fever and a dry cough for several weeks and then slowly improved, but the cough persisted. She went to work, changing positions frequently because her cough disturbed other workers. About a year later, she began to expectorate small amounts of a thick, creamy sputum.

She was seen in the Respiratory Clinic at Rush Medical College, in February, 1924, when she was 18 years of age. A diagnosis of nontuberculous abscess of the lung and bronchiectasis was made. Repeated examinations of the thick, creamy, almost odorless sputum showed numerous masses of fine bacilli-like structures. Attemps to grow this organism on all types of mediums failed at this time, and as the patient did not improve under medical management, she was sent into the hospital to have the abscess drained. Her temperature seldom rose above 99.2 F., and the blood and urine were normal. Following this operation, her general condition improved, and she gained some weight, but six

months later she returned to the hospital to have drainage reestablished. Further attempts to determine the type of organism were made at this time, with the following results.

Granules were not observed in the sputum. Smear preparations contained many slender rods with rounded ends, about 5 microns in length and one-half micron in width (figs. 1 and 2). Some filamentous forms, but no clubs or branching forms, were present. The bacilli were generally arranged in clumps and were not motile. The organism took ordinary stains, was not acid-fast and

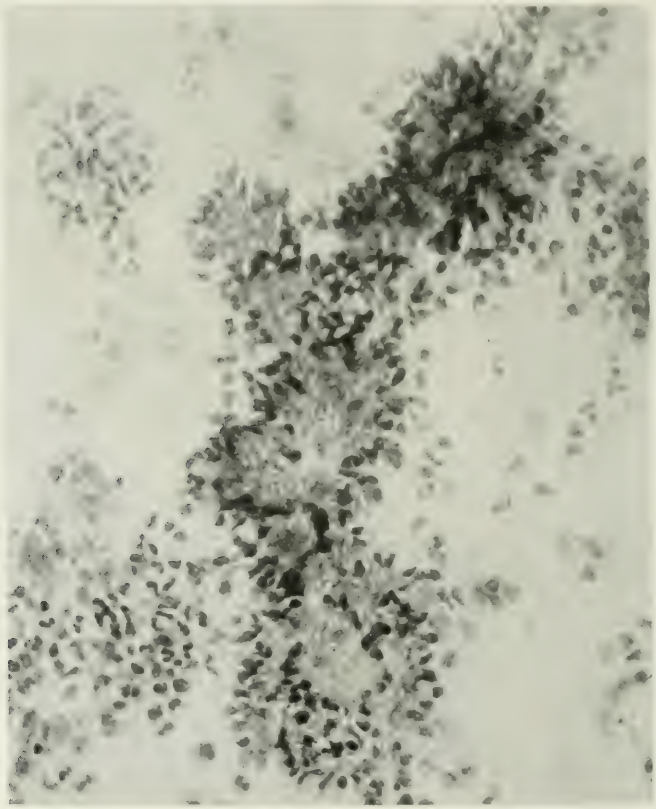


Fig. 1.—Smear preparation from sputum, showing masses of rods surrounded by cells (Giemsa stain); × 250.

was granular, the granules retaining the Gram stain. When first examined, these masses of bacilli were observed, but at that time they were not surrounded by cells. Two years later, they were often found encircled by a single or by several layers of epithelial cells mixed with polymorphonuclear leukocytes. This arrangement may have been due to the necrosis of the bronchial cells. Usually, a variable number of eosinophil leukocytes were present.

The organism was an anaerobe, growing best at about 36 C. but also slightly at room temperature. Growth appeared generally in from twenty-four to forty-eight hours after incubation. It was difficult to grow the organism, which did

not grow on blood agar or on ordinary culture mediums. The most favorable medium for its cultivation was Bacto-malt extract agar (synthetic) and malt extract agar with and without chalk. Growth rarely appeared on the surface of the agar, but when colonies did form they were of a deep cream color, soft, with regular edges and were about 1 mm. in diameter. In shake cultures growth appeared below the surface, the colonies were lenticular and varied from the size of a pin-point to 1 mm. in diameter. The organism grew in the form of tiny balls in the fluid of condensation. A little gas was sometimes produced.

The associated streptococci died out rapidly on the maltose medium, so that the bacilli were easily isolated in pure culture.

In cultures the organism appeared as rods with rounded ends, varying from 5 to 10 microns in length and from one-half to one micron in width (figs. 3 and 4).

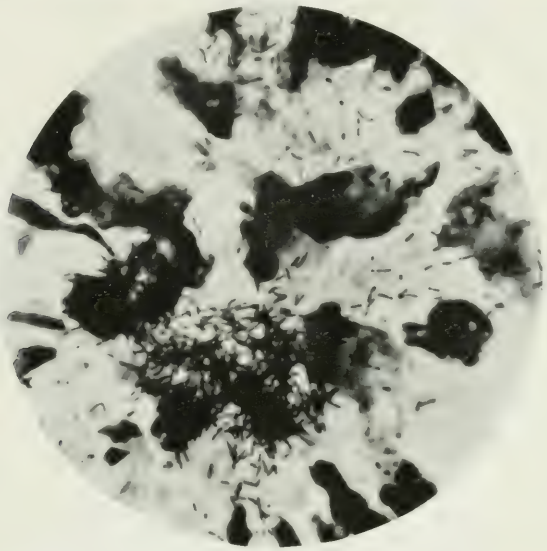


Fig. 2.—Smear preparation from sputum showing rods (carbolfuchsin stain); × 1,200.

The bacillary forms appeared singly or in palisade arrangement, the central part staining deeply, with swollen unstained ends. Some organisms had swollen ends containing deeply staining bodies. Rosette formation was rarely seen on the surface of agar, but was usual in the fluid of condensation. The rods often had swollen, unstained club-shaped ends and appeared to radiate from a central granular mass. Branching was frequent, the buds appearing to come from deeply staining bodies. Spores were not demonstrated. The organism was not motile. The body of the rod was gram-negative, the granules retained the stain. It was not acid fast and stained with ordinary dyes.

Pure cultures of this bacillus, injected intravenously into a rabbit and intraperitoneally into guinea-pigs and mice, did not produce any lesions one month after inoculation.

This organism differs from the actinomyces usually described in not producing macroscopic granules and clubs in the tissues, and differs culturally in readily producing clubs which resemble the actinomyces clubs seen in tissues.

According to Castellani (*New Orleans M. & S. J.* **79**:20, 1926), this organism seems to belong to the class of fungi of the genus *Nocardia*. The condition in the lung seems to correspond to the agranular bronchonocardiasis described by Castellani as a serious type of bronchomycosis which runs a chronic course, does not generally respond to treatment and ends fatally.

Fig. 3.—Forty-eight hour growth of pure culture in fluid of condensation of malt agar (Giemsa stain); × 1,000.

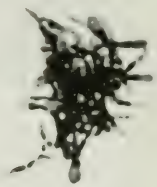


Fig. 4.—Forty-eight hour growth of pure culture in fluid of condensation of malt agar (Giemsa stain); × 1,200.

Summary—A case of agranular bronchonocardiasis is described. The sputum contained masses of slender gram-positive rods and filaments, which did not branch or form clubs. The organism grew anaerobically on mediums containing malt, showed branching and club-shaped ends and often appeared in rosette-like masses.

May 9, 1927.

SARCOMA OF THE FEMALE BREAST

A. J. PETERSEN

From the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago

Sarcoma of the female breast is a rare tumor. The older statistics place its frequency at about 10 per cent of all tumors of the female breast, but recent figures are from 2 to 3 per cent. The reclassification and the more refined microscopic diagnostic technic in use at the present time are unquestionably responsible for this disease. Thus Poulsen (*Arch. f. klin. Chir.* **42**:593, 1891), in 1891, found that sarcoma constituted about 9.3 per cent of all mammary tumors; Williams (Connell, F. G.: *Surg. Gynec. Obst.* **4**:13, 1907), in 1894, 3.9 per cent; Gebele (*Beitr. z. klin. Chir.* **29**:167, 1901), in 1901, 9.1 per cent; Finsterer (*Deutsche Ztschr. f. Chir.* **86**:352, 1906-1907), in 1907, 6 per cent; Bloodgood (Rohdenburg, G. L.: *Proc. New York Path. Soc.* **17**:112, 1917), in 1908, 2.01 per cent; Rodman (Diagnosis of Mammary Tumors, *J. A. M. A.* **56**:793, [March 18] 1911), in 1911, 2.7 per cent; Geist and Wilensky (Sutton, G. D.: *J. Michigan M. Soc.* **15**:190, 1916), in 1915, 3.9 per cent; Rohdenburg (*Proc. New York Path. Soc.* **17**:112, 1917), in 1917, 2 per cent; Deaver and McFarland (The Breast: Anomalies, Diseases, Treatment, Philadelphia, P. Blakiston's Son & Company, 1917, p. 372), in 1917, 2 per cent; Winslow (*Ann. Surg.* **74**:341, 1921), in 1921, 2.94 per cent.

The spindle cell type of breast sarcoma is the most common; it formed 68 per cent of the 156 sarcomas in Gross' (*Am. J. M. Sc.*, 1887, pp. 17, 94, 120) series, 32 per cent of the 34 in Gebele's series, and 23 per cent of the 43 in Finsterer's series. Deaver and McFarland found 206 spindle-cell sarcomas among 838 sarcomas of the breast collected from the literature up to 1917.

A summary of the reports of thirty-seven spindle-cell sarcomas of the female breast recorded in the literature from 1900 to 1925 yields the following information. (Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1919, p. 485. Graves, T. C.: *Brit. M. J.* **1**:81, 1920. Hyde, F. C.: Tumors of the Mammary Gland, *J. A. M. A.* **34**:773 [March 31] 1900. Jessup, D. S. D.: *Proc. New York Path. Soc.* **19**:117, 1919. Jopson, Speese, and White: *Ann. Surg.* **48**:662, 1908. Lee, B. J.: *Ann. Surg.* **72**:387, 1920. L'Esperance, E.: *Proc. New York Path. Soc.* **17**:112, 1917. Liell, E. N.: *South. M. J.* **1**:392, 1908. Ricketts, E.: *Am. J. Obst.* **44**:689, 1901. Rosenstein, P.: *Arch. f. klin. Chir.* **63**:555, 1901. Shere, O. M.: *Colorado M. J.* **11**:49, 1914. Speese, J.: *Ann. Surg.* **49**: 428, 1909). One tumor occurred in a negro, aged 50, the others in members of the Caucasian race between the ages of 14 and 98, 66 per cent of them in women below the age of 50. The average age at which the patient first observed the tumor was 42. Fourteen of the women were married, three single, three widowed; the social condition was not given in seventeen instances. Childbirth was mentioned in the histories of less than half the married and widowed women. Etiologically, heredity played no part, while trauma was recorded in four instances. The left breast was involved in twelve cases, the right in fifteen, the position was not stated definitely in ten. The outer half of the breast was occupied by six of the eleven tumors of which the exact location in the breast was described. At first the tumor was described as a "very small lump," "pea-sized," etc. Twenty of the tumors grew slowly or remained for a period of from one to thirty-seven and one-half years, and there was rapid growth from the beginning in four. E. Ricketts reported a tumor which remained quiescent for thirty years and then grew to the size of a child's head in five months fol-

lowing a severe attack of influenza, which left the patient prostrated. The sarcoma attained the size of a walnut in seven instances, of a fist in ten instances, and of a child's head or larger in twenty instances. Five of the tumors were multiple; the rest were apparently single. The smaller growths were usually firm; the larger were soft and frequently contained fluid, cystic degeneration and hemorrhage. The tumor was fixed to the skin in six cases, to the pectoral muscle in three, to the thorax in two. The nipple was retracted once, and yielded a secretion or discharge in only one case. There was discoloration of the skin of the breast in seven patients, dilatation of the superficial veins of the breast in nine patients, ulceration of the breast over the tumor in nine patients. Pain appeared in the breast either early or late in sixteen instances. The axillary lymph glands were enlarged in four of the women, the supraclavicular in one. Actual infection of the lymph glands was demonstrated in only one patient prior to or at the time of the first operation. Nine tumors had capsules, but they were not always intact.

Thirty-one patients were operated on, with known recurrence of the growth in five. Three of the tumors recurred in from two to three months, two of them in from four to five years. Metastases appeared in seven patients, five of whom had not had local recurrence following operation, and one of whom had not had an operation. The lungs were involved in three cases, the liver in four. The following organs were affected, each in one instance: brain, thyroid, ribs, mediastinum, wall of the heart, lungs, great omentum, liver, both kidneys, left ovary, pancreas, mesenteric lymph glands, vertebral bodies, muscle of the right thigh, left axillary glands, supraclavicular glands and right inguinal glands. Seven patients died following operation because of recurrence or metastasis, whereas in an equal number neither condition occurred for periods of from one and one-half to twenty-four years. The average duration of life of the former patients from the time of the initial appearance of the tumor until death was ten years; from the time of the beginning of rapid growth until death, three years. Eight patients were said to have suffered emaciation, weakness and cachexia. Seventeen other spindle cell sarcomas of the female breast (mentioned in the bibliography quoted) reported from 1900 to 1925 are not included in this summary because of insufficient data in the reports.

The first of two sarcomas of the breast reported here occurred in a well nourished, married white woman, aged 44. She was struck on the right breast in an automobile accident, and a week later noted a small lump. There was no pain at any time, but the lump gradually increased. After about two months, examination revealed two firm, freely movable nodules in the upper outer quadrant of the right breast, the largest about the size of a small orange, the other one half that size. There was no retraction of the skin of the breast or axillary adenopathy. The patient gave a history of one childbirth. A clinical diagnosis of fibro-adenoma of the right breast was made. The right breast and axillary nodes were removed in the service of Dr. L. L. McArthur, and following an uneventful recovery, the patient was given a series of roentgen-ray treatments. She is living and well four and one-half years after the appearance of the tumor.

The pathologic report (Edwin F. Hirsch) was as follows: This was a recently amputated breast with a little axillary fat, forming a tissue 30 by 16 by 6 cm. in its maximum dimensions. On the upper side was a diamond-shaped piece of skin, 19 by 7 cm. with a nipple, and in the deeper tissues were two firm masses, 6 by 5.5 cm. in their greatest dimensions. The nodule first mentioned was firm, white and translucent, with a thin capsule; the other was also firm, white in places, but mostly yellow. Lymph glands in the axillary region were as large as 2 cm. in their greatest dimensions. Microscopic examination of the tumors showed infiltrating bands and dense masses of fibrous

tissues in which there were many immature spindle-shaped and irregularly shaped cells and nuclei (fig. 5). Sections of the lymph glands did not contain this tissue.

The second tumor occurred in a well-nourished, married white woman, aged 31, who had noted a small nodule about the size of an egg in the upper portion of her right breast for about eight years. This nodule began to grow more rapidly, and in a few months attained the size of an orange. The right breast was amputated in the service of Dr. W. J. Hurley, and following an uneventful recovery the patient was treated by the roentgen ray over a period

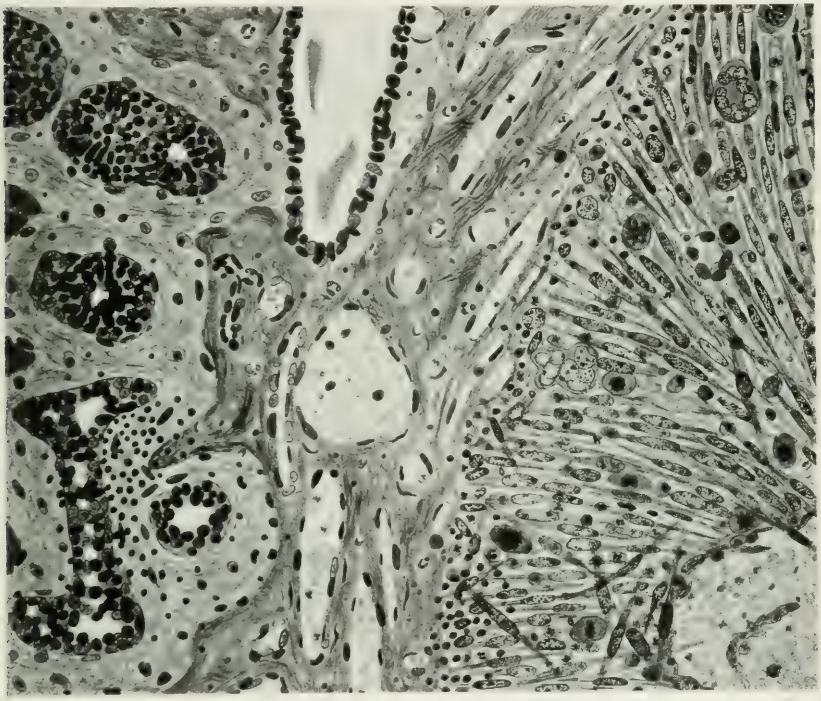


Fig. 5.—Spindle-cell sarcoma of the breast.

of about a year. The patient was living and well two years after the beginning of rapid growth. She had never been pregnant.

The pathologic report (Edwin F. Hirsch) was as follows: This was a recently amputated female breast forming a mass of tissue when spread out about 18 by 16 by 4 cm. On the upper side was an oval piece of white skin 19 by 8 cm., with a nipple. In one place there was a tear in the tissue of the breast about 8 cm. in diameter. The lining was scarred and torn fibrous tissue. Adherent to the lining were masses of white edematous fibrous tissue from 1 to 3 cm. in diameter. On the outside of these tumor masses was the normal substance of the breast. Inside were three separate edematous pieces of white and blood-stained tissue 8 by 2 by 4.5 cm., 6 by 4 by 2 cm. and 3.5 by 2.4 by 2 cm. Sections across these pieces showed edematous white tissue mottled about 20 per cent with dark red hemorrhages. Sections of the tissue masses in the cystlike place contained edematous fibrous tissue. Portions of it were necrotic,

other portions densely hyalinized. Widely scattered ducts lined with a simple columnar epithelium were found in all of these tissues. These ducts did not have the appearance of infiltrating tissue. In some of the sections the tissues were cellular, but of the connective tissue variety and seemed to be in active growth.

According to Deaver and McFarland, most mammary sarcomas are well encapsulated at first, because they usually arise through the sarcomatous transformation of benign tumors. He supports this theory by three arguments: 1. A small tumor exists in the breast for a long time, then takes on a rapidity of growth out of all proportion to the previous rate of growth and often attains great size. 2. Mammary sarcomas are well encapsulated and freely movable during the early part of their existence, while sarcomas elsewhere in the body are barely surrounded by a definite membranous capsule. It is therefore concluded that mammary sarcomas derive their capsules from the benign, antecedent tumors from which they grow. 3. Mammary sarcomas are commonly described as adenosarcomas, adenocystic sarcomas or other forms, and the occurrence of epithelial glandular elements in their structure may be accounted for by supposing that they develop in tumors of glandular structure, many of whose elements persist in spite of the sarcomatous change of the connective tissue.

On the other hand, there is the relatively rare sarcoma which arises directly from the connective tissue of the breast and begins as a small tumor that grows steadily and rapidly. It rarely attains great size. Ulceration of the skin occurs early. Metastasis to the internal organs is less common than in the first type of sarcoma described. Of the thirty-seven patients whose cases are summarized above, there were four in whom the tumor displayed immediate rapid growth, and it may be noted that metastasis occurred in but one of these.

The differential diagnosis of sarcoma of the breast is often difficult. The small recent mobile sarcoma may be taken for a fibro-adenoma, and the diagnosis depends on the histologic examination of the tumor tissue. An ulcerated sarcoma with axillary adenopathy may be mistaken for a carcinoma; but a large firm tumor of recent rapid growth, without the usual retraction of the nipple, the usual fixation of the surrounding tissues and the usual axillary involvement, should suggest sarcoma rather than carcinoma, according to Gross. The spindle cell sarcoma may be differentiated from the round cell and the giant cell sarcoma by its development at a comparatively early age, its slow recurrence after removal and the long life of the patient. The round cell sarcoma occurs at a comparatively late age, recurs rapidly, and the duration of life is relatively short. The giant cell sarcoma likewise appears late in life, but the duration of the life is remarkably long, and local recurrence is delayed longer than in the other types.

May 9, 1927.

SERIAL

RB
1
C45
v.12

GERSTS

Chicago Pathological Society
Transactions